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STUDY 3[3]		"excellent"			
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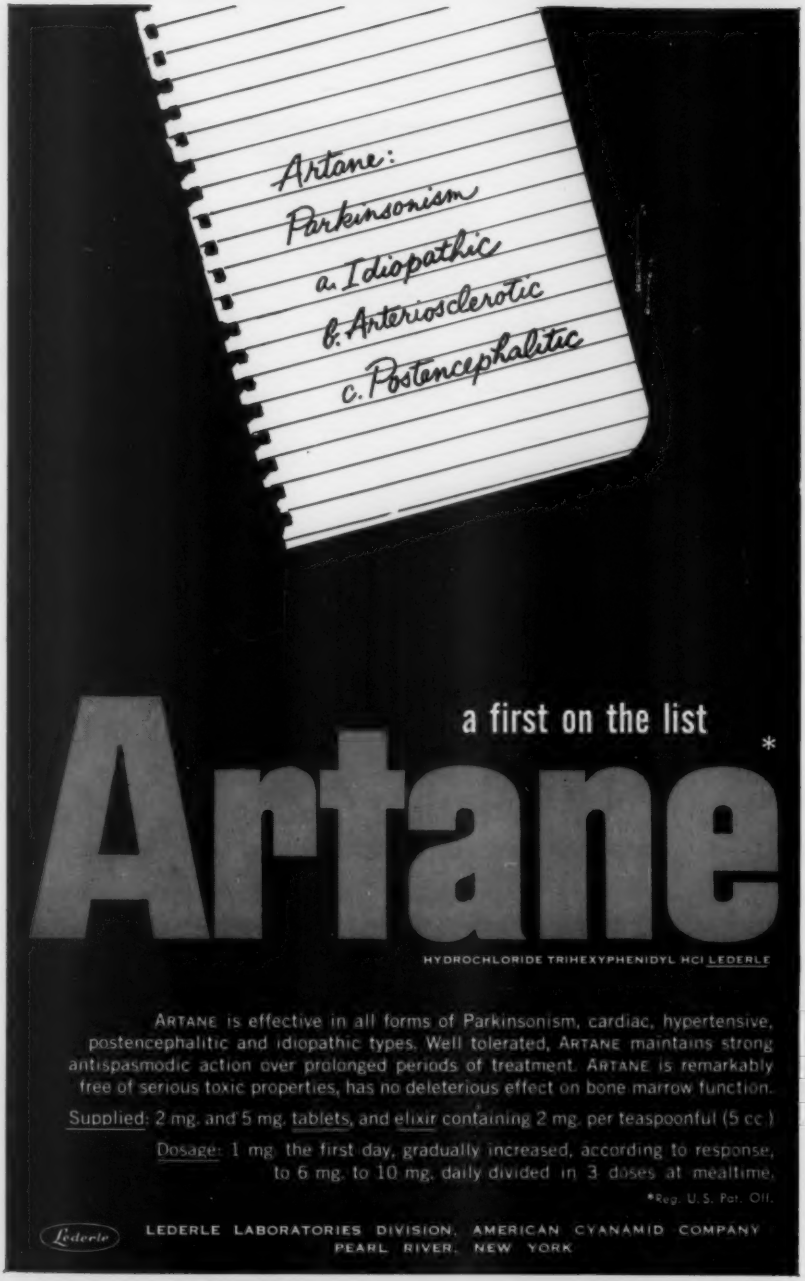
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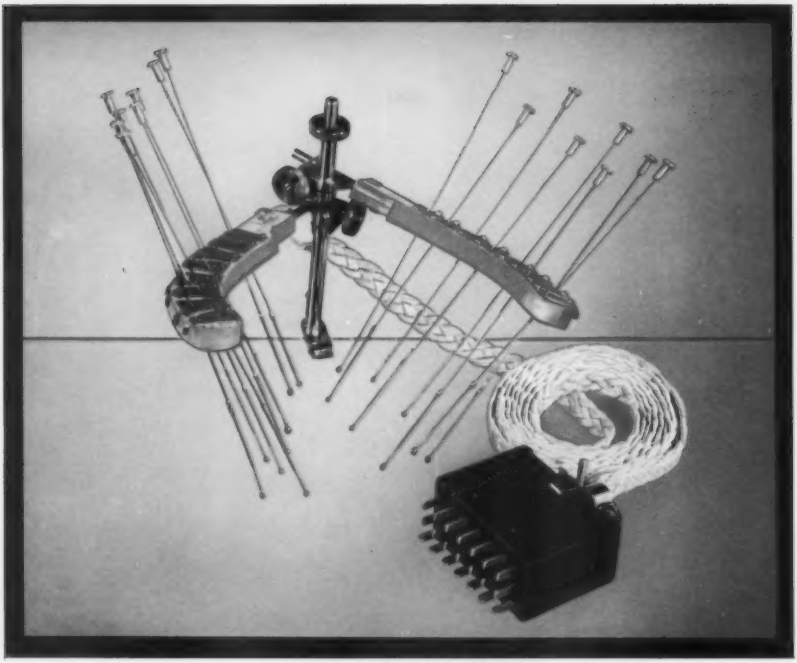

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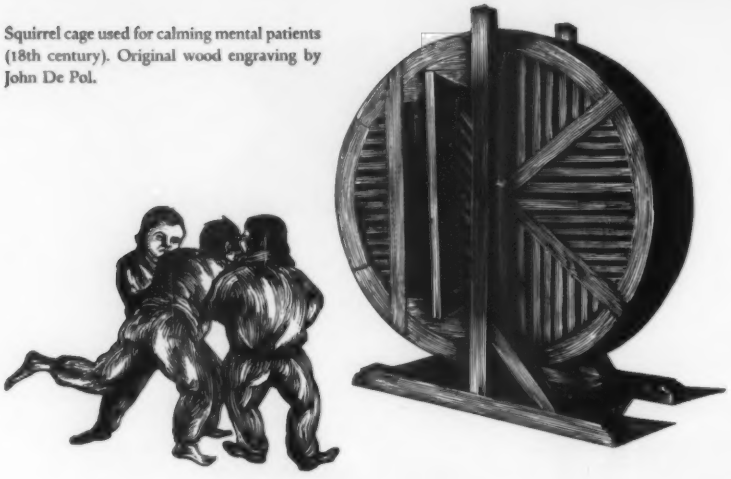

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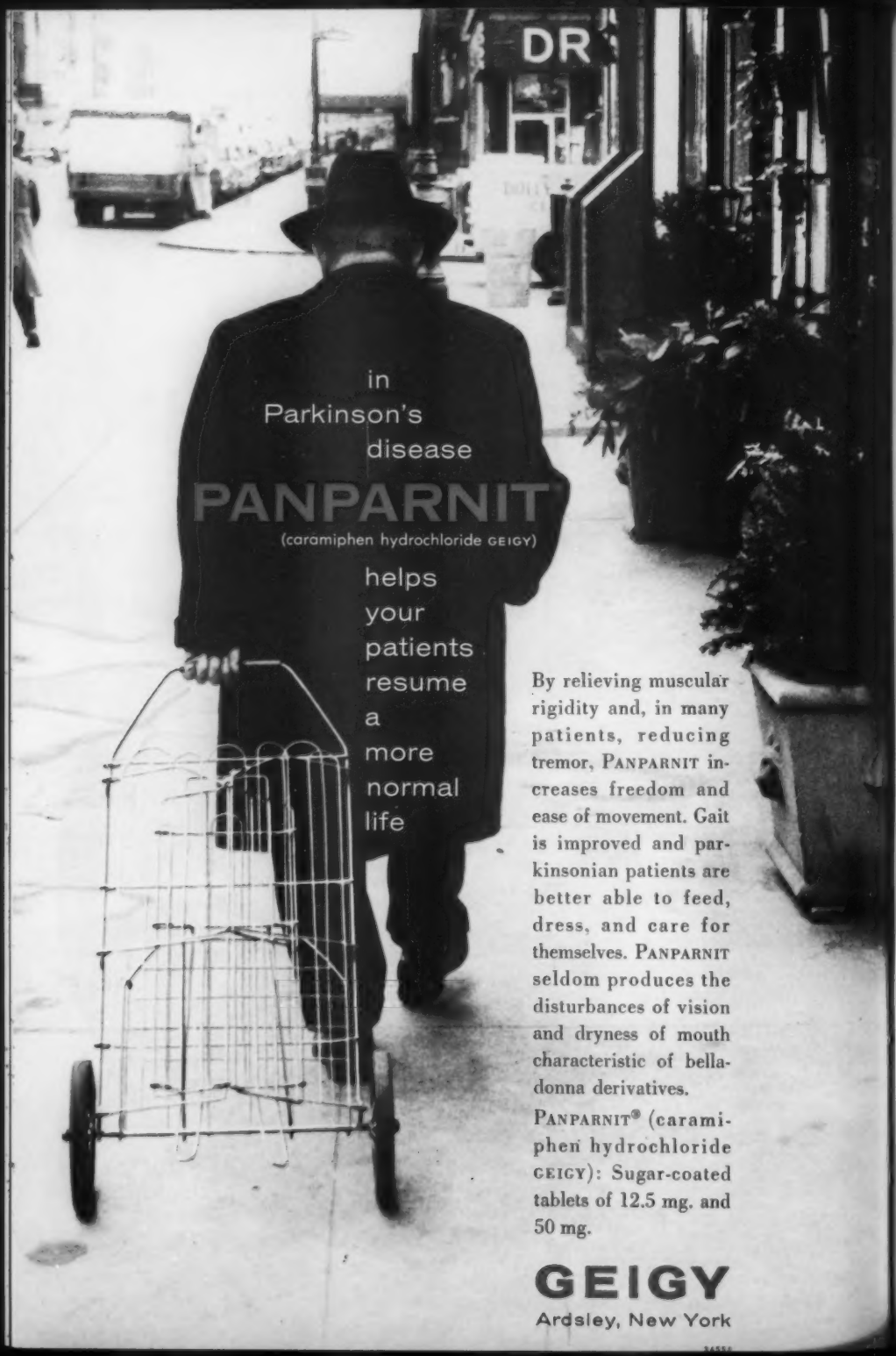

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Studies on the "cerebral pacemaker"

Robert B. Aird, M.D., and Bill Garoutte, M.D.

ONE OF THE BASIC principles underlying the neurologic examination concerns the comparison of homologous parts and depends upon the bilateral symmetry of the human organism. Because one side of the body may serve as a control for the other, relatively minor abnormalities may be detected by means of a careful and direct comparison of homologous structures. That this same principle might be utilized in the electroencephalographic examination was suggested by the essential anatomic symmetry of the two cerebral hemispheres and has been confirmed by the routine detailed analysis of thousands of clinical electroencephalograms in our laboratory and elsewhere. The technic of electroencephalography in use at the University of California School of Medicine at San Francisco was developed with the express purpose of systematically exploiting this basic principle and depends upon the simultaneous recording of homologous areas of the scalp.[1–4]

With the simultaneous recording of homologous areas, it immediately became apparent that the homologous runs of brain waves not only were essentially similar in size, form, and frequency, but that a striking degree of hemispheric synchrony was maintained. This, however, was not an original observation, inasmuch as the synchrony of homologous brain waves was an early observation in the history of electroencephalography and, in fact, has been commented upon by several investigators.[5–8] In spite of these observations, surprisingly little has been done to explain the mechanism by which the synchrony of the two hemispheres is mediated. In attempts to throw further light on this question, studies have been underway in our laboratory over the past five years which initially involved a quantitative examination of the degree of synchronism of both normal and abnormal brain waves. These studies have led us to postulate a central neurophysiologic mechanism, through whose activity the electroencephalographic rhythms of the two hemispheres were synchronized. This mechanism has been termed "the cerebral pacemaker." The concept is not entirely new, as various investigators have from time to time suggested that some such mechanism must be present to account for the observed synchrony.[9,10]

The present paper is intended to present the essential data and concepts that have been developed on this subject and to offer additional supporting material from the analysis of the electroencephalogram.

MATERIALS AND METHODS OF STUDY

The new material reported herein was derived from the study of several groups of subjects.

The first group consists of 20 patients selected from a sequential run of 500 routine (3 cm./sec.) tracings in the electroencephalographic laboratory. Selection was limited to

From the departments of neurology and anatomy and the electroencephalographic laboratory, University of California Medical Center, San Francisco, California.

Read at the tenth annual meeting of the American Academy of Neurology, Philadelphia, April 25, 1958.

records showing long runs of slow-wave activity (3 to 6 cps.) with smooth tops so that the peak of the wave could be determined with accuracy. Study showed that an accuracy of plus-or-minus ten milliseconds, or about one-third millimeter, could be obtained in properly selected records. The relative lag of one homologous wave with respect to its counterpart from the opposite hemisphere was measured. A series of such measurements taken in sequence was then plotted, as shown in figure 1. From these same studies, the over-all degree of synchronism from runs of 20 or more waves in sequence were collected for comparison with other types of cerebral activity (table 1 — "slow wave" group).

The second group under study consisted of eight subjects with widespread normal alpha activity of smooth contour. Series of scalp electrodes were arranged linearly from side to side across the posterior half of the head, as illustrated in the sketch of figure 2. Simultaneous paper recording from all the electrodes applied versus a cervical reference electrode was performed at the most rapid paper speed available (6 cm./sec.). Using the peaks of corresponding homologous waves as a reference, the relative asynchronism of a series of 20 or more waves was determined and the differences were plotted, as in figure 2. It was possible to determine the peak of individual waves with an accuracy of plus-or-minus five milliseconds with the rapid paper speed.

The third group studied consisted of two patients with pneumoencephalograms showing the classical roentgenographic findings of agenesis of the corpus callosum. From both of these patients suitable runs were recorded from the occipital leads with the use of a DuMont double-beam oscilloscope and a 35 mm. moving-film camera operated at a rate of 50 cm. per second. With this type of recording, accuracies within plus-or-minus one millisecond were possible. Figure 3 shows a plot of the relative synchrony of a series of homologous waves from one of the agenesis patients when measured in the same fashion as indicated above.

Lastly, we were able to perform oscillographic studies on an eight month old baby with prominent and constant 20-per-second fast activity. This activity was, of course, interpreted as grossly abnormal. Nevertheless, it is of considerable interest that this baby, the youngest on whom we have had the opportunity to do adequate oscillographic studies, showed the same degree of homologous synchronism (figure 4) that we have observed with normal alpha and beta activity.[11]

The relative synchrony of each group studied is summarized in table 1, as well as similar data with respect to our study of the normal alpha and beta waves[11] and the two types of spikes from the material utilized in an earlier study.[12]

As described in detail in the earlier investigations cited, the studies of alpha and beta activity and of spikes were performed using the double-beam oscilloscope and moving-film camera, as mentioned above.

OBSERVATIONS

The most interesting observation derived from a study of the first group of patients concerns the clear demonstration (figure 1) that sequences of homologous pairs of slow waves

TABLE 1
DEGREE OF SYNCHRONY OF HOMOLOGOUS EEG RECORDINGS

Type of Recording	*Number of Subjects*	*Number of Measured Waves*	*Synchrony*		
			Per Cent Within 1 msec.	*Range (in single subjects)*	*Per Cent Within 5 msec.*
Alpha	47	1,676	55%	10 to 90%	73%
Beta	7	648	52%	26 to 67%	79%
Petit mal spikes	14	756	34%	6 to 58%	68%
Other spikes	10	307	41%	17 to 89%	68%
Agenesis of corpus callosum	2	458	48%	38 to 54%	70%
Slow wave	20	759	21%	7 to 35%	30%

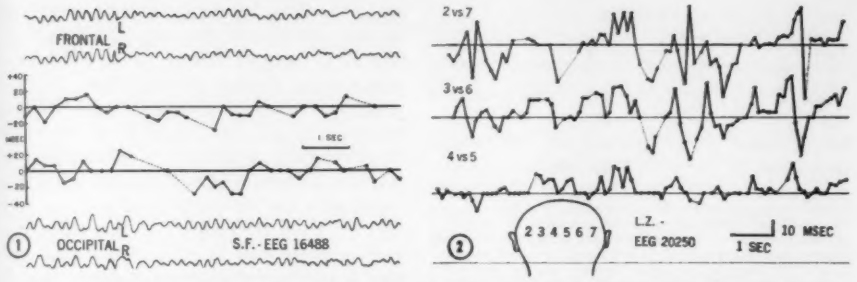


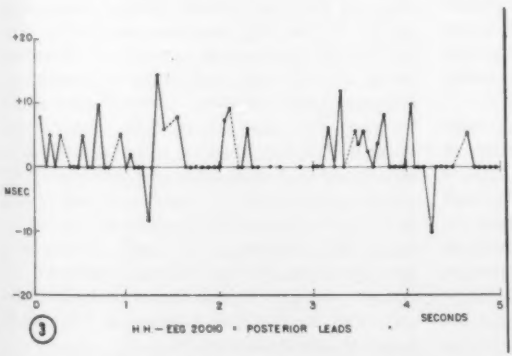
FIG. 1. Patient S. F., age one year, convulsive. Six per second sinusoidal activity recorded at 3 cm. per second from frontal and occipital regions simultaneously. The plotted points represent the measured differences between times of occurrences of the electroencephalographic waves; the upper plot from the frontal tracing, the lower plot from the occipital tracing. Points are plotted above the zero line if the right-sided wave occurs earlier than the left-sided wave, and vice versa.

FIG. 2. Patient L. Z., age 13 years. Ten per second alpha activity recorded at 6 cm. per second from electrodes arranged linearly across the occiput, 3 cm. apart. The three plots represent the measured variations in synchrony between homologous regions of right and left sides. Upward deflection means right-sided wave occurs earlier than left.

show exactly the same sort of pseudo-rhythmic variation around the point of perfect synchrony that we found with both spiking activity and the normal alpha and beta activity.[11,12] This is of considerable interest, inasmuch as it extends our observation of an essentially similar pattern of synchronism to still another type of cortical activity not previously included in our observations.

The two graphs of figure 1 make it clear that the majority of homologous waves are nearly synchronous and, when not, they show a definite and consistent tendency to return to a synchronous state. Since this same observation has been made with respect to every sort of electrocortical activity we have studied, some source of rhythmic control outside of the cortex itself would appear to be essential. The demonstrated "synchronophilic" tendency of the brain waves would seem particularly to support the concept of a subcortical pacemaker.

Figure 2 presents additional information on the synchrony of alpha activity. Through the use of rapid, multiple-channel paper recording, it has been possible to study the alpha rhythm



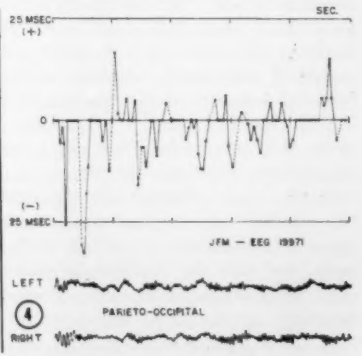


FIG. 3. Patient H. H., age 15 years, agenesis of the corpus callosum. Plot of measured variations in synchrony between right and left occipital regions; activity at 18 cps. Upward deflection means right-sided wave occurs earlier.

FIG. 4. Patient J. F. M., age eight months, mentally defective. Plot of measured variations in synchrony between right and left parieto-occipital regions; abnormal activity at 20 cps. Upward deflection means right-sided wave occurs earlier than left.

TABLE 2

Type of Recording	*Statistical Likelihood of Perfect Synchrony*	*Actual Incidence*
Alpha	2%	53%
Beta	4%	52%
Petit mal spikes	Less than 1%	34%
Other spikes	Less than 1%	41%
Slow waves	2 to 5%	21%

The statistical likelihood of perfect synchrony is calculated by dividing the average wave length of the waves being studied into the range of experimental error of measurement. For example, for alpha activity, the average wave length is about 100 msec., and the accuracy of measurement is plus-or-minus 1 msec., yielding a quotient 2 msec./100 msec. = 2%, which represents the statistical likelihood that two waves would be measured as synchronous if they occurred completely randomly.

from several areas of the scalp simultaneously and thus to compare the plots of synchrony of homologous pairs of alpha waves recorded at exactly the same time. Figure 2 shows that the same pseudo-rhythmic variation of synchrony is present in all homologous pairs of waves, regardless of the area studied.

If the general contour of the three plots in figure 2 are compared, that is, the plots of "2 vs. 7," "3 vs. 6," and "4 vs. 5," it will be observed that their patterns are more or less parallel. Thus, when one plot lies above the line of perfect synchrony – the right-sided wave peak is earlier than the left – the same relationship is true of all three plots. This parallelism between the plots of different areas suggests that each hemisphere acts to a certain extent as a unit. The deviations from perfect parallelism, which are considerable at times, might be accounted for in terms of a transient escape of the intrinsic rhythms of the cortex from the influence of the "pacemaker."

From figure 2, then, it is possible to conclude that the pseudo-rhythmic variation of hemispheric synchrony is present in all homologous areas observed simultaneously, that the two hemispheres show some tendency to operate rhythmically as partially independent units, and that the rhythms of widely separated areas of the cortex, when studied simultaneously, appear to be influenced by a common factor (pacemaker) so that they return toward synchrony at the same time.

It was of particular interest that the studies performed on patients with agenesis of the corpus callosum (figure 3) showed the same pseudo-rhythmic plots of hemispheric synchrony as found in the studies reported previously. In the presence of the corpus callosum it is logical to suggest that a direct influence of one cortical rhythm on the other might be mediated by the association tracts of this large structure, which thus could be of importance in determining synchrony. Considerable work has been done to suggest that such a functional connection via the corpus callosum is possible.[13,14] The demonstration of synchrony in even a single case in which the corpus callosum is lacking would seem to prove that this structure is not essential to the regulation of interhemispheric synchrony. On the other hand, the evidence cited does not prove the converse, namely, that the corpus callosum may not be a significant pathway for the transmission of impulses between the hemispheres under certain conditions.

Figure 4 has been included because of the recent interest reflected in the literature regarding brain maturation. The plot of relative synchrony-asynchrony found in this eight month old infant is indistinguishable in general form from plots similarly obtained from adults. This suggests that the pacemaker matures at a relatively early stage, and implies that the mechanism concerned is a phylogenetically primitive one.

DISCUSSION

A central neurophysiologic mechanism capable of regulating the synchrony of the brain waves of the two cerebral hemispheres is suggested by the high incidence of perfect synchrony found with both normal and abnormal forms of brain-wave activity in our studies on humans. Animal studies by the Morisons and Dempsey,[15–17] by Jasper and Droogleever-Fortuyn,[18] and by Moruzzi and Magoun[19] have established that central neurophysiologic mechanisms exist which are capable of influencing cortical electroencephalographic activity bilaterally and diffusely. That such mechanisms may be responsible for bilateral synchrony, as observed in our clinical studies, has also been suggested in the observations of Obrador,[20] Jasper,[21] and Rasmussen.[22]

Evidence for a Central Pacemaker

A number of observations may be cited which support the concept of a central pacemaker mechanism. At the same time some of these observations minimize the probable con-

tribution of the corpus callosum to the maintenance of bilateral synchrony of the electroencephalogram.

Firstly, from the data summarized in table 1, it is seen that from one-third to more than half of the homologous pairs of waves, regardless of their type, occur within one millisecond of perfect synchronism. The significance of this observation is emphasized by noting that the occurrence of perfect synchrony of homologous waves on the basis of chance could be expected to occur but rarely (table 2).

Inspection of table 2 makes it apparent that there is no possibility of accounting for the degree of synchrony found on the basis of chance occurrence. A mechanism capable of regulating the synchronism of the two cerebral hemispheres, therefore, may logically be postulated to explain the observed data.

Studies of the intrinsic rhythm of the cortex[23–28] and of the intrinsic rhythms of the thalamus[29–31] have shown that the latter are generally more rapid than the former, as would be required for the effective control of cortical rhythms by thalamic rhythms.

Additional evidence in favor of a central pacemaker has been obtained from a study of patients with gross electroencephalographic foci.[32] In most of these patients, with focal cerebral pathology clearly evidenced by clinical findings and gross electroencephalographic foci, diffuse bilateral dysrhythmias were found. Such generalized dysrhythmias have not usually been limited to, or even more marked in the homologous region on the side opposite to the pathologic lesion, as would be expected if the disturbance spread via the corpus callosum. In contrast to the focal asynchronism observed directly over the focus in 97 per cent of cases, the generalized dysrhythmias observed in these same cases were found to be essentially synchronous. This would appear to preclude the possibility that the abnormal activity on the pathologic side preceded that on the opposite side, as might be expected if the spread were via commissural pathways. In fact, such generalized dysrhythmias have shown a pseudo-rhythmic pattern similar to that noted above for many other types of brain-wave activity, as in figure 1. It is not clear how abnormal electroencephalographic activity arising from a focus on one side could directly influence the opposite cortex to give rise to such a shifting asynchrony from side to side about the point of perfect synchrony. On the other hand, the phenomenon might be accounted for if it were possible for the pathologic focus to disturb a central mechanism capable, in turn, of influencing the entire cortices of both hemispheres from below. Gastaut[10] has hypothesized a mechanism very similar to this in explanation of certain bilaterally synchronous abnormal rhythms. It is worthy of note that, in addition to the diffuse projection systems postulated from the pacemaker bilaterally to both hemispheres, the influence of a pathophysiologic focus upon the pacemaker would, in turn, require efferent pathways from the cortex to the central pacemaker mechanism. Such efferent connections have recently been observed experimentally.[33]

Direct evidence has been obtained in experimental and clinical studies where the corpus callosum is not present. Several studies[34–37] have shown that section of the corpus callosum frequently has no significant effect on the electroencephalogram. Jasper and Droogleever-Fortuyn[18] presented a case in which section of the corpus callosum did not significantly alter the bilateral synchrony of a generalized wave-and-spike pattern.

Our own oscillographic studies of two patients with pneumoencephalographic evidence of agenesis of the corpus callosum showed the same degree of synchronous activity as in patients with intact corpora callosa. From table 1 it is seen that 48 per cent of the pairs of waves whose synchrony was studied were synchronous within plus-or-minus one millisecond, an incidence which exceeds the chance likelihood of synchrony by a factor of ten- or twenty-fold (table 2). Also, the plot of synchrony of sequential waves in figure 3 shows the same sort of pseudo-rhythmic alteration of synchrony as observed in individuals with intact corpora callosa.

Although the data reviewed support the concept of a central pacemaker, as indicated before, this does not mean that the trans-cerebral association pathways have no significant function. It is possible that one hemisphere actually does influence the other directly via the corpus callosum, though the significance of this influence remains undetermined.

Evidence on the probable site of the pacemaker

The studies already cited[15–19] suggest the thalamus or reticular formation of the brainstem as likely locations for the pacemaker mechanism. In human beings, however, it would appear that the thalamus can be eliminated, since the thalami are not connected from side to side across the midline in about 30 per cent of humans, a fact which would not be consistent with the high degree of synchronization observed in all the patients studied. The experimental evidence thus suggests that the pacemaker is probably located more deeply, either in the posterior hypothalamic-subthalamic area or the closely adjacent reticular formation of the upper brainstem. The nucleus reticularis thalami might serve as the final projection nucleus[38–41] through the diffuse thalamic projection system to the cortices of both hemispheres.

The findings in a previously reported patient[12] are also pertinent to this discussion. The patient (J.P.) was a seven year old boy who had a large left-sided porencephalic cyst that was opened at surgery because of an associated convulsive disorder. Preoperative oscillographic studies showed bilaterally synchronous precentral spiking. During surgery, spikes were recorded both from the lip of the cyst in the precentral area and from the depths of the cyst in a region interpreted as directly overlying the left thalamus. These spikes appeared synchronous with the precentral spikes by electrocorticograms obtained in the usual fashion with electroencephalographic ink writers. Since the precentral synchronism by oscilloscopic study had been so excellent and the point of recording in the floor of the cyst was somewhat off the midline, it was felt that the spikes recorded at this point were probably not directly at the source. It was concluded that the synchronous, precentral spiking in this patient, although related to the spiking recorded from the region of the left thalamus, must have had a deeper, essentially midline origin. Excision of the diseased left precentral cortex resulted in the cessation of all spiking from the area excised, from the thalamic region, and from the homologous right precentral area. It appeared in this case not only that was there a deep central mechanism capable of regulating the synchronism of the homologous precentral spiking, but also that this mechanism must have been triggered by the abnormal influence of the left pathologic cortex.

The observation of Bremer[24] that waves may be picked up simultaneously from thalamus and cortex would be in accordance with our findings in patient J.P., again suggesting that a deeper location for the pacemaker is necessary.

Probable nature of the pacemaker

The concept of a central pacemaker in no sense implies that the various rhythms regulated by it have their origins in the pacemaker mechanism itself. Rather, the pacemaker might be conceived of as a physiologic mechanism which is readily susceptible to rhythmic influences from the cortex, and in turn capable of influencing the cortex diffusely, that is, in areas beyond the point where the original rhythm may have arisen. Furthermore, it would appear that such a mechanism of mutual interaction should be postulated, regardless of whether the rhythms under consideration were normal or abnormal. Thus might be derived a unifying concept whereby many or even most generalized wave patterns derive their rhythms from a mutual interaction between cortex and pacemaker.

In the case of the alpha rhythm, where thalamocorticothalamic reverberating circuits were at one time postulated, it has been shown that the electrochemical characteristics of individual neuronal membranes may provide a suitable basis for a rhythm of approximately ten per second.[42] Although reverberating circuits are not entirely ruled out, probably the intrinsic cortical rhythms are synchronized by the rhythmic influence of the diffuse projection system of the thalamus, which connects the reticular formation of the midbrain to the cerebral cortices. Variations of synchrony then would result from the tendency of the intrinsic cortical rhythm to escape from the control of the subcortical pacemaker. This would adequately explain the pseudo-rhythmic shifting of the leading wave from side to side, as observed in our studies.

Another explanation for the shifting asynchronism observed might be postulated on the basis that the intrinsic rhythm of the pacemaker itself was variable, either because of

physiologic exhaustion of neuronal circuits[43] or on some other basis. Since this would imply that the pacemaker had a firm control over cortical rhythms, it seems less likely than the explanation offered in the previous paragraph.

The data given and the neurophysiologic explanations considered make it clear that a rigid regulation of hemispheric synchrony comparable to the pacemaker of the heart is not contemplated. The intrinsic rhythms of the right and left cortices possess considerable local autonomy, but are evidently maintained in or close to synchrony (within the limits observed) by the physiologic action of a center connected to both hemispheres.

Electroencephalographic implications of the pacemaker concept

If the pacemaker concept is valid, lesions which interfere with the projection paths anywhere between the brainstem and cortex could act to disrupt the cortical synchronism of the areas affected. Focal asynchrony indeed is found in such cases, provided the homologous recordings are obtained simultaneously. In thousands of localization studies, we have found asynchronism of homologous runs to be a valid component of the abnormal electroencephalogram and to be present in association with focal lesions in a high percentage of such cases. Our evidence permits the conclusion that focal asynchronism is as useful a criterion of focal abnormality as the out-of-phase activity of a focus obtained by linear or triangulation methods of recording. Since all the technics mentioned sample the same underlying phenomenon, they should and usually do give similar results. The direct comparison of homologous tracings obtained simultaneously is probably more appropriate as it more nearly parallels the bilateral anatomic and functional symmetry of the brain.

Our observations suggest that the pacemaker mechanism is unique and that all types of diffuse cortical activity, whether normal or abnormal (slow wave, wave and spike, diffuse spikes, or other), are controlled by the same anatomic and physiologic mechanism. In the occasional cases where generalized dysrhythmias are essentially asynchronous, either diffuse pathology must be postulated, as advocated by Jasper and Kershman,[9] or deep pathology disrupting the function of the pacemaker mechanism itself must be considered.

Clinical significance

As has been mentioned earlier, generalized electroencephalographic changes may be produced by the influence of pathologic processes in the cortex. If the concept of a central pacemaker is correct, such generalized dysrhythmias should improve following adequate resection of the focal pathology. Improvement following such resections is well known and has been observed to be particularly striking in cases with severe and extensive pathology, as in our patient J. P. or where hemispherectomy has been done.

Not only does the electroencephalographic pattern improve following such procedures, but the patient's clinical status may improve as well. Thus, seizures, behavior disorders, and mental slowing may be benefited by surgery in well selected and favorable cases.

As suggested by the above considerations, the pathophysiologic characteristics of focal cerebral lesions are manifested by both clinical and electrophysiologic findings that may be correlated one with the other. This being the case, electrophysiologic methods of study, in conjunction with the clinical investigation of the patient, might well lead to the establishment of proper criteria for the selection of cases suitable for neurosurgical resection of focal cerebral pathology.

CONCLUSIONS

1. The degree of synchronism of several types of brain waves has been determined by the simultaneous recording of homologous runs from the two cerebral hemispheres. High-speed photographic recording (50 cm./sec.) of oscillographic tracings were required for the study of normal alpha and beta activity and rapid rhythms, including spiking of various types. Paper recordings at 3 cm./sec. or more rapid rates were used in the study of slow-wave activity.

2. More than 50 per cent of the waves studied were found to be synchronous within the limits of accuracy of the method of measurement: plus-or-minus one millisecond with oscillographic studies and plus-or-minus five to ten milliseconds with paper recording. The degree of asynchrony of all types of brain-wave activity was observed to change from

moment to moment, with leading of the waves first on one side, then on the other, varying in a pseudo-rhythmic fashion about the point of perfect synchrony.

3. These findings, together with other evidence adduced, have been interpreted as favoring a central neurophysiologic mechanism which is capable of regulating the rhythms of both hemispheres simultaneously. This has been termed the "cerebral pacemaker." Studies of synchrony in patients with agenesis of the corpus callosum, as well as other evidence, tend to minimize the role of this pathway in the maintenance of synchrony.

4. The pacemaker is most likely located in the reticular substance of the upper brainstem or in the adjacent posterior hypothalamic region, and it probably functions via a relay through the nonspecific diffuse projection nuclei of the thalamus.

5. Modification of the pacemaker function through the pathophysiologic influence of unilateral focal lesions was supported by the findings in an operative case. This and other evidence were considered in explanation of the synchronous generalized dsyrhythmias frequently associated with focal lesions, as well as bilaterally synchronous spiking. The generalized wave-and-spike activity of petit mal variant cases, and probably of most classical petit mal cases as well, is probably mediated by the same mechanism.

6. The essentially synchronous character of all types of brain-wave activity observed, except that directly overlying electroencephalographic foci, confirms the value of focal asynchronism as a valid component of the pathophysiology of focal cortical lesions. This type of asynchrony is believed to result when the lesion anatomically and/or functionally severs the overlying cortical area from its connections with the central pacemaker.

7. The correlative value of electrophysiologic studies (oscilloscopic, as well as electroencephalographic) with the clinical manifestations, commonly observed in patients with cerebral pathology, were discussed. The possibility was suggested that physiologic criteria in this group of cases might be established, which in conjunction with the clinical data could be used in the proper selection of patients for neurosurgical intervention.

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■ There are three motor symptoms which may occur with tumour of the cerebellum; they have their analogues in cerebral disease. (a) Reeling. (b) A certain resisting rigidity. (c) Tetanus-like paroxysms. Reeling, I think, is, or at least depends on, a cerebellar paralysis, the analogue of the hemiplegia, a cerebral paralysis; persistent rigidity is the analogue of the well-known rigidity in hemiplegia, and the tetanus-like seizures of unilaterally beginning convulsive seizures from cerebral cortical disease. After some unilaterally beginning convulsion there is temporary paralysis of the parts first and most convulsed. I have yet no facts as to anything analogous in cerebellar disease.

J. Hughlings Jackson in *On Tumours of the Cerebellum*, published in 1881.

Promising results in cryptococcal meningitis

Harry Rubin, M.D. and Michael L. Furcolow, M.D.

CRYPTOCOCCAL MENINGITIS, long considered a rare and fatal infection, is being reported with increasing frequency in the recent medical literature.[1] Whether this represents a true increase in incidence or a greater awareness on the part of the practicing physician cannot be clearly determined at the present time. Certainly, fungus infections have assumed a more prominent place in the differential diagnosis of infectious diseases. The use of broad spectrum antibiotics, the broadened applications of steroid therapy, and the increasing use of cytotoxic drugs may all contribute to this renaissance in medical mycology.

The natural course of cryptococcal meningitis is characterized by exacerbations and remissions and, therefore, evaluation of therapy is difficult. Recently, favorable results have been reported with the use of a new antibiotic, amphotericin B.[2] This antibiotic, shown to be fungicidal in vitro,[3] has also been shown to be very promising in therapeutic trials against several of the deep mycotic infections.[4] This report concerns our experience in the treatment of ten cases of cryptococcal meningitis with amphotericin B.*

MATERIALS AND METHODS

C. neoformans was isolated from the spinal fluid of all patients and also from skin lesions of two patients. All clinical specimens were cultured on Sabaraud's dextrose agar at 37° C. and at room temperature. Simultaneous intracerebral mouse inoculations were performed. Pathogenicity of all isolated strains of *C. neoformans* was confirmed by the demonstration of capsule formation and growth of budding yeast forms at 37° C. Nine of the ten isolated strains were also shown to be pathogenic for mice, with the development of a hydrocephalus in seven to ten days. Encapsulated budding yeast forms of *C. neoformans* could be demonstrated directly in India-ink preparations from brain material. The strain isolated from the cerebrospinal fluid of case 10 was shown not to be pathogenic for mice using the above criteria.

Amphotericin B was administered intravenously in all patients. The dosage ranged from 50 to 100 mg. daily and approximated 1 mg. per kg. of body weight. This amount of drug was dissolved in 1 liter of 5 per cent glucose and water and administered over a minimum of six hours. Intravenous injections were given daily or every other day. Total doses varied between 1.4 and 3.7 gm. of amphotericin B in the eight surviving patients.

CASE REPORTS

Case 1. A 31 year old white female became ill seven months prior to therapy. Her chief complaints were fever and severe constant headaches, with periods of disorientation. These symptoms became progressively worse over the succeeding months. She was treated with a total of 2.65 gm. of amphotericin B over a nine-week period. Her spinal fluid has converted to normal and 14 spinal fluid specimens obtained since the onset of therapy have been sterile for fungi. At present, 13 months after treatment, she is asymptomatic and back to her normal activities.

Comment. This patient, with a 13-month follow-up and repeatedly normal spinal fluid, represents the most likely instance of a "cure" in this series of cases.

Case 2. A 37 year old white male had rheumatoid spondylitis (1942) and lymphosarcoma (1950). He was treated with steroids for his arthritic complaints, and shortly therafter he developed skin lesions on his back and behind his ear. These failed to heal. He then developed meningeal signs, with headache, confusion, and photophobia. Shortly after this he was also given a course of nitrogen mustard as treatment for his lymphosar-

*A preliminary report concerning some of these cases was presented at the Fifth Annual Symposium on Antibiotics held in Washington, D. C., Oct. 2-4, 1957.[5]

From the Kansas City Field Station, Communicable Disease Center, Bureau of State Services, Public Health Service, U. S. Department of Health, Education, and Welfare, University of Kansas Medical Center, Kansas City, Kansas. Read at the tenth annual meeting of the American Academy of Neurology, Philadelphia, April 25, 1958.

coma. *C. neoformans* was cultured from his spinal fluid and skin lesions. A total of 1.4 gm. of amphotericin B was administered intravenously. The skin lesions healed in 17 days. Eight subsequent spinal fluid specimens have been sterile for fungi and the last lumbar tap revealed a normal spinal fluid. He is now well and asymptomatic 13 months after therapy.

Comment. This patient has a lymphoma proved by biopsy and also received steroid and nitrogen mustard therapy. All three of these factors may have been related to his subsequent cryptococcal infection.

Case 3. A 62 year old white male farmer had an illness of five years' duration. Over the years his illness was characterized by personality changes, diplopia, and staggering gait and more recently by repeated vomiting and severe headaches. He received a total of 1.85 gm. of amphotericin B over a ten-week period. Seven spinal fluid specimens have been sterile for fungi. Ten months after therapy he was asymptomatic except for mild residual headaches. Now, 11 months since treatment, he has had a clinical relapse, with dizziness, staggering gait, and headaches. Two more spinal fluid specimens obtained recently, however, have remained sterile.

Comment. This case represents a treatment failure with clinical relapse, although repeated spinal fluid specimens have remained sterile. He is being given a second course of therapy with amphotericin B.

Case 4. A 31 year old white male had both Hodgkin's disease (1944) and tuberculosis (1948), the latter requiring bilateral orchiectomies. He developed a papule on his forehead and an abscess with a draining sinus on the chest wall. Cultures of material taken from these lesions revealed *C. neoformans.* He was treated with sulfadiazine for six weeks; he was then given 15 daily 225 mg. ampules of 2-hydroxystilbamidine with no change in his condition. Shortly after this he developed meningeal signs and bilateral papilledema. He was treated with a total dose of 3.7 gm. of amphotericin B over a four-month period. His symptoms and skin lesions cleared within five weeks. Spinal fluid findings are completely normal and 12 repeated lumbar taps have yielded sterile fluid on culture. Ten months after therapy, however, his skin lesions have recurred.

Comment. This case represents another instance of the observed association between cryptococcal infections and lymphoma. The recurrence of skin lesions indicates the persistence of infection, although the spinal fluid remains normal and he has no symptoms referable to the central nervous system.

Case 5. A 45 year old colored male had central nervous system disease of long standing. He first noted the onset of persistent headaches in 1946. Over the next few years he developed weakness and incoordination of his legs, which progressed to a spastic paralysis of his lower extremities by 1949. He was also proved to have pulmonary tuberculosis at this time. *C. neoformans* was cultured from his spinal fluid in 1950 and 1956. He was treated with oral and intramuscular amphotericin B and then given a total of 2.6 gm. of drug intravenously. In addition, he received five 1 mg. intrathecal doses given every third day. Spinal fluid protein and cell counts have improved, and the spinal fluid has been sterile on 11 subsequent lumbar taps. His clinical condition and neurologic findings are unchanged.

Comment. This patient's clinical condition was stable prior to therapy. He was placed on amphotericin B in the hope of sterilizing his spinal fluid. This was accomplished. No significant changes could be expected in his long standing neurologic abnormalities.

Case 6. A 63 year old white male farmer had had diabetes for five years. He had not been feeling well for the previous six months but had no specific complaints. One month before the onset of treatment he developed headaches, nausea, extreme fatigue, and nucchal rigidity. The patient showed a changing state of consciousness over the next few weeks, alternating between coma and semicoma, but his course was progressively downhill. He was give amphotericin B for seven days with no change in his course and he expired on the seventh day of treatment. Autopsy revealed a chronic meningitis and *C. neoformans* was cultured from the brain and spinal fluid. His diabetes had been well controlled during the entire terminal illness.

Case 7. A 51 year old male began complaining of headaches 11 months before treatment. These persisted and became more severe shortly prior to admission to the hospital. He became increasingly lethargic and was admitted to the hospital in deep coma. His pupils were fixed and unequal and he responded only slightly to painful stimuli. He received 780 mg. of amphotericin B and expired after two weeks of therapy without regaining consciousness. Autopsy revealed exudate over the meninges and base of the brain, with numerous clusters of cryptococci in the meninges on microscopic examination.

Comment. Cases 6 and 7, although treatment failures, were both moribund and in coma prior to therapy and received very short courses of therapy.

Case 8. A 52 year old white male had been ill for four months prior to therapy. At this time he received an accidental blow on his head, after which he began complaining of severe headaches. These persisted and he also noted diplopia and "dizzy spells." After admission to the hospital he was observed to be disoriented for place and time. All of these symptoms abated except for his "dizzy spells" and he was in a clinical remission at the time therapy was begun. However, culture of his cerebrospinal fluid was positive. He received a total dose of 2.4 gm. of amphotericin B, but therapy was stopped after one month because of evidence of hepatic toxicity. His 45-minute bromsulfalein retention rose to 23 per cent and a

liver biopsy revealed diffuse inflammatory changes. At the present time, three months after therapy, he is completely asymptomatic and no longer complains of dizziness. Seven spinal fluid specimens have been sterile for fungi since completion of therapy.

Comment. This is the only case in which treatment had to be stopped because of apparent drug toxicity.

Case 9. A 64 year old white male became ill eight months prior to therapy, with severe headaches, fever, weakness of one leg, and bilateral papilledema. He was treated with 2.8 gm. of amphotericin B. He showed moderate clinical improvement, although the spinal fluid remained abnormal. Four months after treatment the spinal fluid revealed *C. neoformans* on culture after eight consecutive spinal fluid specimens had been negative on culture.

Comment. This case is the only one of the surviving cases in this series whose spinal fluid revealed *C. neoformans* by culture following the completion of therapy. He is now being treated again.

Case 10. A 60 year old white male began experiencing neck pain ten months before treatment. This was followed by anorexia, fatigue, and occasional diplopia. He ran a low-grade temperature during this time. Treatment consisted of a total of 2.2 gm. of amphotericin B. At the present time, two months after therapy, he is asymptomatic. His spinal fluid has improved and has remained sterile on six consecutive cultures.

Table 1 summarizes the results of treatment in all ten cases. Eight of the ten patients are alive, wtih follow-ups ranging from two to 14 months. The two fatal cases were both moribund and in coma prior to treatment and never regained consciousness during short courses of therapy. Two patients (cases 1 and 2) are back to their normal activities and have normal spinal fluids which have remained sterile on repeated cultures. Three patients (cases 4, 8, and 10) have shown clinical improvement, with either normal or improved spinal fluid indices. Their spinal fluids have remained sterile. The clinical status of case 5, who had long standing central nervous system disease, has remained stable, although his spinal fluid has been found sterile on 11 occasions over a nine-month period. Two patients (cases 3 and 9) have had a relapse. Case 3 has had a recurrence of symptoms; however, the organisms have not been recovered from his spinal fluid. Case 9, although showing moderate clinical improvement, has had *C. neoformans* cultured from his spinal fluid on two occasions after eight spinal fluid specimens had been sterile. Both of these patients continue to show high cell counts, high protein, and low glucose in the cerebrospinal fluid. Both are having a further course of therapy with amphotericin B.

Toxic side reactions to amphotericin B did occur but were not serious. Chemical phlebitis

TABLE 1

CASES OF CRYPTOCOCCAL MENINGITIS TREATED WITH INTRAVENOUS AMPHOTERICIN B

			Pre-Treatment*		Post-Treatment			
Case	*Age*	*Sex*	*Clinical Status*	*Duration*	*Clinical Status*	*Length of Follow-up*	*Spinal Fluid Findings*	*Spinal Fluid Culture*
1	31	F	Poor	7 months	Normal activities	13 months	Normal	0 (14)
2	37	M	Poor	3 months	Normal activities	13 months	Normal	0 (8)
3	62	M	Poor	5 years	Relapse	14 months	Abnormal	0 (9)
4	31	M	Critical	4 months	Improved	10 months	Normal	0 (12)
5	45	M	Paraplegic	10 years	Unchanged	9 months	Improved	0 (11)
6	63	M	Moribund	1 month	Expired	—	Abnormal	+
7	51	M	Moribund	11 months	Expired	—	Abnormal	— (Positive on section)
8	52	M	Fair	4 months	Improved	3 months	Improved	0 (7)
9	64	M	Poor	8 months	Moderate improvement	4 months	Abnormal	+ (Relapse)
10	60	M	Poor	10 months	Asymptomatic	2 months	Improved	0 (6)

*All cases had abnormal spinal fluids with positive cultures for *C. neoformans* prior to treatment.

occurred when the drug was administered too rapidly, but this could be avoided by sufficient dilution and administration of the drug over a six-hour period. Febrile reactions with chills and occasionally nausea and vomiting accompanied the initial intravenous infusions. These could be diminished or avoided by premedicating the patient with aspirin or an antihistamine and repeating this during the intravenous administration.

Transient elevations of the blood urea nitrogen occurred in three patients (cases 2, 8, and 10). These occurred with the higher dosages and returned to normal levels after withdrawing the drug for a few days. There were no other signs of renal toxicity accompanying these rises and therapy was reinstated in all cases when the blood urea nitrogen dropped to normal levels.

Therapy was stopped in case 9 due to apparent liver toxicity. This is the only case in this series with this complication.

DISCUSSION

The often reported association of cryptococcal meningitis and lymphomas[6,7] was also observed in this small series. Two patients had lymphomas (cases 2 and 4), one having a lymphosarcoma and the other, Hodgkin's disease. The lymphomatous disease antedated the cryptococcal infection by 8 and 12 years, respectively. In addition, two patients had concomitant tuberculosis and one had diabetes mellitus.

The survival time of untreated cryptococcal meningitis has varied from two weeks[8] up to 16 years[9] from the time of diagnosis. This point is illustrated by cases 3 and 5 whose illnesses began five and ten years before, respectively. *C. neoformans* was cultured from the spinal fluid of case 5 seven years before treatment was instituted.

The evaluation of therapy must certainly be approached with caution in any infection which can occasionally remit for years. Although such remissions do occur, the usual course of this infection is characteristically progressive to a fatal termination. A recent monograph on the subject states that 80 to 90 per cent of patients die within the first year and that the usual duration of the untreated illness is approximately six months.[1] The survival of eight out of ten patients in this series for periods ranging from two to 14 months after treatment suggests that the treatment did have an effect on survival.

Apparent cures in single cases of cryptococcal meningitis have been reported in the literature. Marshall and Teed[10] obtained excellent results in a patient following bilateral mastoidectomy and sulfadiazine therapy. Wilson and Duryea[11] reported the successful use of actidione in one case of cryptococcal meningitis. Subsequent reports concerning this agent have failed to confirm these successes.[12–14] This emphasizes the need for further studies with adequate follow-up in evaluating therapy.

Amphotericin B has been shown to be extremely effective in experimental cryptococcal infections produced in mice.[15] Prolonged survival time has been demonstrated with different dosage levels by both the oral and intraperitoneal routes of administration.[16] Recently, application of the tissue culture method in this laboratory for the evaluation of antifungal agents[17] has also shown amphotericin B to be fungicidal against *C. neoformans* in concentrations as low as 0.1 microgm. per ml. With the use of this method as a screening tool, this antibiotic was shown to be the most promising among several agents for use in cryptococcal and several other fungal infections.

Blood level determinations, using a modification of a bioassay technic described by Littman,[18] revealed "adequate" levels following intravenous administration of the drug when compared with in vitro inhibitory levels.* These levels persisted for up to 48 hours; therefore, administration on alternate days with a dose of 1 mg. per kg. of body weight was considered feasible. Very low or absent levels following oral administration make this route of only questionable value. There were no demonstrable amphotericin B levels found in the spinal fluids following intravenous administration. Although this seems paradoxical, the fact remains that spinal fluid specimens were repeatedly found to be sterile for fungi. Perhaps only low levels, which are not measurable by the above method, are required to be effective. In vitro tests have shown that the drug is inhibitory against *C. neoformans* in 33

*Blood level determinations were performed under a grant from the Squibb Institute of Medical Research.

per cent spinal fluid at levels one-half to one-third those needed for similar inhibition in broth, serum, or urine.[16] This suggests that a lower level of drug is needed in spinal fluid than blood to be as effective.

The most promising finding in this series of treated cases was the consistent cultural sterility of the spinal fluids in seven of the eight surviving patients. With the exception of case 9, lumbar taps repeated six to 14 times have been sterile on culture and following animal inoculation. This objective finding lends confidence to the definite impression that treatment has prolonged the lives of the eight surviving patients. It certainly provides more assurance than an analysis of clinical status in this chronic and occasionally remitting type of meningitis.

The relapse occurring in two patients and the recurring skin lesions in a third patient indicate that therapy in these cases did not eliminate the infection. It would seem, however, that infection of the central nervous system was eliminated in case 4, since his spinal fluid remains normal despite the recurrence of skin lesions. Since clinical experience with amphotericin B is still quite limited, it is difficult to determine what an adequate course of therapy should be. With this in mind, these patients are being retreated. The emergence of resistant strains of *C. neoformans* must also be considered as a possible explanation for these treatment failures. There have been no reports concerning resistance of strains of *C. neoformans* to amphotericin B. Recently, Littman[19] has reported on the emergence of resistant strains of *Candida* after repeated subcultures in a medium containing amphotericin B. Studies performed on the re-isolated strain of *C. neoformans* from case 9, however, showed no change in its sensitivity to amphotericin B when compared to the original isolate.

Consistent side reactions, although troublesome, did not necessitate cessation of treatment in any of the cases. A rising blood urea nitrogen should be watched for. Since no other evidence of renal toxicity was found, treatment was reinstituted in all cases after levels had returned to normal. The reason for this rise in blood urea nitrogen is unknown at this time.

The finding of hepatic abnormalities in one patient deserves some comment. Diffuse inflammatory changes were seen on microscopic examination of a liver biopsy. Although this was temporally related to the drug administration, other causes should be considered. Viral hepatitis might be considered; however, the patient did not demonstrate any of the usual clinical or laboratory findings of this infection. Cryptococcal infection of the liver may have been responsible, although no yeast-like organisms were seen on the biopsy sections. Hepatic toxicity has not been noted in previous reports concerning amphotericin B, including a recent extensive summary covering its use in 19 of 60 treated cases of deep mycotic infections.[4]

The findings in this report do not warrant any definite conclusions. Adequate follow-up and further clinical trials are necessary. At the present time, however, amphotericin B seems to be the most promising agent available in the treatment of cryptococcal meningitis.

SUMMARY

Ten cases of cryptococcal meningitis treated with intravenous amphotericin B are presented. Eight patients are alive after follow-ups ranging from two to 14 months. The most promising finding was the consistent sterility of the spinal fluids in seven of the eight surviving patients. No definite conclusions are warranted from this small series of cases beyond the fact that amphotericin B does seem to be the most promising agent now available in the treatment of this infection and that further trials are justified.

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■ Galen says, that in the early part of his life he had seen an epileptic boy, about thirteen years of age, who spoke of this affection as a certain something which he could not clearly describe, ascending along the thighs, the loins, the sides, and the neck, up to the head; which was followed by a total loss of memory or recollection. He also mentions a case, in which the sensation was compared to that of a cold wind ascending to the head. Paulus Ægineta likewise describes this *aura frigida* as going from the legs, or from the fingers to the head. He speaks of a woman who, during pregnancy, had epileptic fits, which were preceded by a sense of a cold air ascending from the uterus to the brain. Schenckius has described this sensation as it affected a boy of twelve years of age, who was subject to epilepsy.

John Cooke in *A Treatise in Nervous Diseases*, published in 1824.

Intracranial pneumoplanigraphy in the verticosubmental position

A neuroroentgenographic refinement

W. Eugene Stern, M.D., William Hanafee, M.D. and Stephan Wilk, M.D.

INDIRECT METHODS of visualizing the intracranial contents are of inestimable value in assessment of disease of this area. Refinements in current technics and the addition of new ones, if safe, should always be welcome. The present paper describes a combination of two well-accepted, neuroradiologic manipulations, each of which is valuable alone and, when combined, may offer additional diagnostic aid.

METHOD

Standard pneumoencephalographic or ventriculographic air contrast methods have been modified to incorporate horizontal planigraphy as part of a radiologic technic whereby, in a series of from four to eight films, the intracranial contents are visualized in a plane approximating a parallel to the undersurface of the cerebral hemispheres.

Ventricular or cerebrospinal fluid is exchanged for filtered gas in the conventional way, either in the operating room or in the radiology department, under whatever narcosis or anesthetic agents are required for a given case.

Immediately following the liquid-gas exchange, the patient is positioned on his abdomen with the head and neck moderately extended (verticosubmental position – figure 1 A and B). In the interests of obtaining as standard a positioning as possible, the patient's chin is rested upon a soft but adjustable pad whereby an imaginary line connecting the nasion with the external auditory meatus lies horizontal on a plane parallel with the surface of the laminagraph table. In the accompanying anatomic study this imaginary line has acted as the baseline, and the laminagraph "cuts" are numbered according to the number of centimeters above this line. Thus, cut number 3 is oriented 3 cm. above the nasion-external auditory meatal plane and so on.

The exposure factors are identical with those required for similar routine views. The milliampere-seconds are so distributed that the x-ray tube will be energized during its entire 40° sweep, which is one second in duration.

Patients with short, thick necks may at times be difficult to posture, as may be those with disease of the cervical spine which prevents full hyperextension.

ANATOMIC-RADIOLOGIC CORRELATION STUDIES

The change in our anatomic orientation, which is required for the correct interpretation of the horizontal planigraphic pneumograms, led to the following study. Two apparently normal, formalin-hardened brains were imbedded in clear gelatin with catheters incorporated in the lateral and fourth ventricles. The ventricular system was aspirated of liquid and insufflated with air. Laminographic "cuts" were made approximating the parallel plane, as previously described, and were numbered at approximately the same levels. The brains were then sliced horizontally at 1 cm. spacings and photographed. The result, a correlative study of radiographic anatomy, is illustrated in figures 4 to 7. The radiographic product presents gas and solid "in depth" and includes more, for example, than can be illustrated in a single, two-dimensional brain slice. The structures, as labeled, represent the composite anatomic reconstruction of at least three

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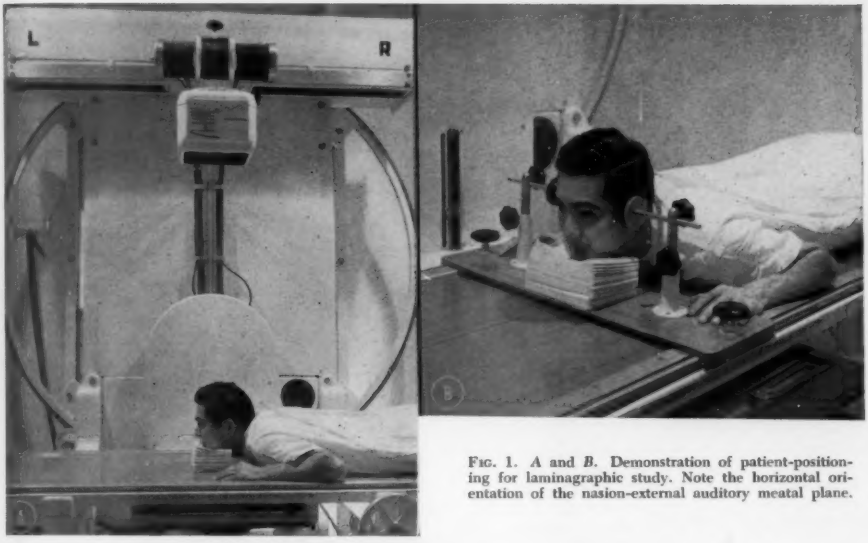

FIG. 1. *A* and *B*. Demonstration of patient-positioning for laminagraphic study. Note the horizontal orientation of the nasion-external auditory meatal plane.

brain slices which bracket the radiologic laminagraphic "slice."

LITERATURE REVIEW

In 1934 Ziedses des Plantes[1] reported the utilization of a combination of pneumographic and planigraphic technics in neuroradiology. In 1937 Carillo, Oribe, and Malenchini[2] recommended tomoencephalography to visualize the midline ventricular system, cerebellum, and basal cisterns; lateral, parasagittal, as well as coronal "cuts" were employed by Turner and Lutz[3,4] and by Manfredi and Kruse.[5] Epstein and Davidoff[6] and Poppel, Jacobson, and Dewing[7] emphasized the value of these combined technics for demonstration of midline structures, as labeled, represent the compogas shadows. The only application of horizontal technics presented in the literature is that reported by Sansone and co-workers[8] in a brief statement of pediatric pneumoencephalographic methods.

DISCUSSION

The development of a three-dimensional, mental picture of intracranial structures is the aim of any interpreter of pneumographic studies. Whereas steroscopy is most helpful in accomplishing this aim, there remains the need to visualize as many structures as possible in two separate projections. The horizontal planigraphic technic permits a view of the ventricular, cisternal, and subarachnoid shadows in a projection familiar to the anatomist and most helpful to the clinician. The accompanying atlas plates highlight the anatomic structures and spaces which are most effectively visualized by these projections.

As an example of the useful definition of pathologic alterations in a structure which otherwise is difficult of visualization by more standard technics, the following case is presented.

CASE REPORT

A six and one-half year old girl was admitted to the University of California Medical Center with a history of generalized convulsive seizures from the age of two months following a hard and difficult delivery. A left hemiparesis had been noted shortly after birth and remained unchanged, as did the major and minor seizures. Standard pneumoencephalography, carried out in April 1956, was supplemented by the current study in which both conventional pneumography and horizontal planigraphic pneumography were utilized. The striking ventricular dilatation on the right side (figure 2 A and B) is correlated well with the clinical deficit, but, more particularly, the latter is further supported by the roentgenographic de-

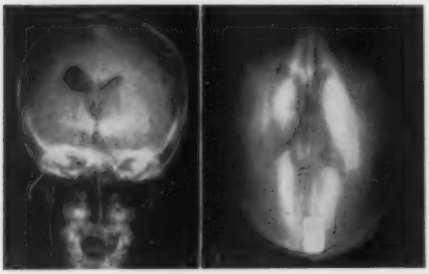

FIG. 2. Comparison of conventtional (*A*) and planigraphic (*B*) visualization of lateral ventricular system of presented case.

FIG. 3. Horizontal planigraphic visualization of brainstem of presented case. Note shrunken cerebral peduncle (arrow) corresponding to enlarged lateral ventricle.

lineation of shrinkage of the cerebral peduncle on the side of the diseased hemisphere as demonstrated in the horizontal view (figure 3).

SUMMARY AND CONCLUSIONS

A variation in the method of combining pneumoencephalography and pneumoventriculography with laminagraphy by utilizing horizontally oriented views has been presented. A neuroradiologic, anatomic correlation demonstrates the advantages of the technic in visualizing intracranial structures in a plane which has been found practical and helpful in clinical application.

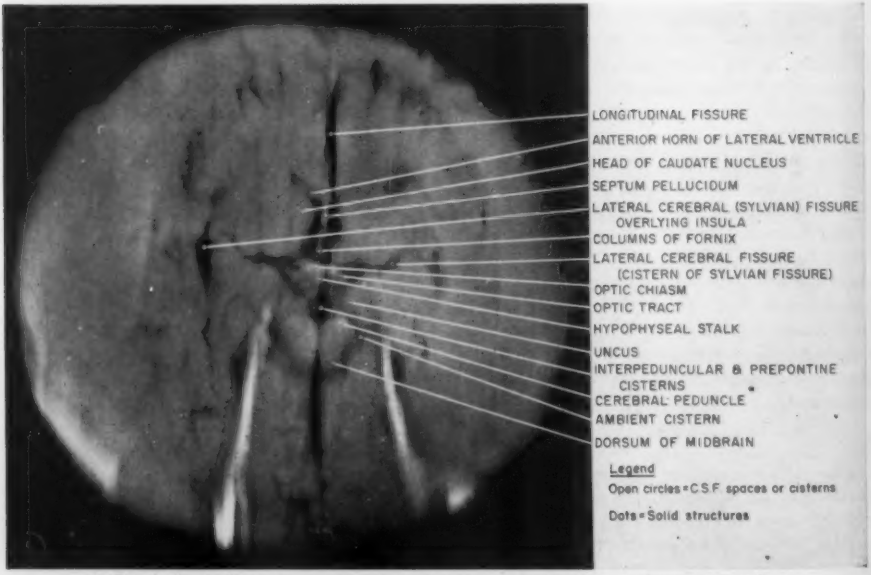

FIG. 4. Anatomic-roentgenographic study of structures visualized 4 cm. above baseline plane.

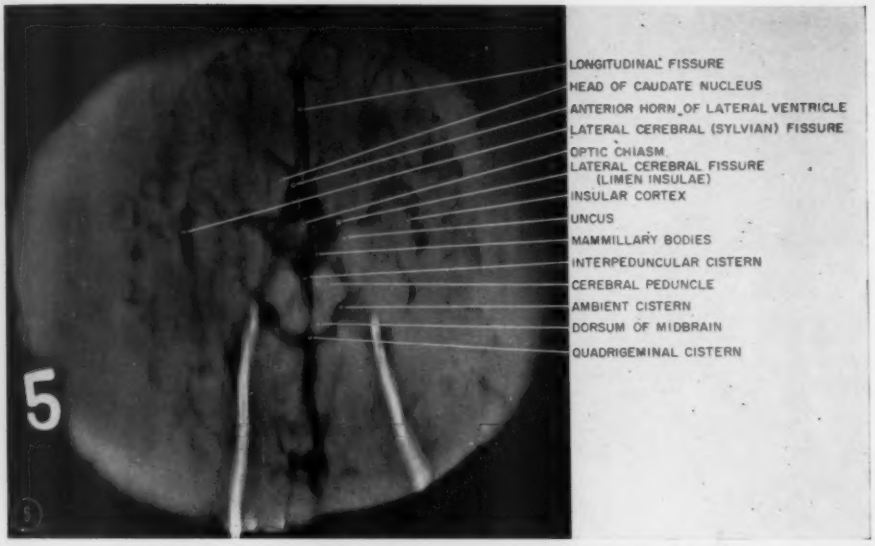

FIG. 5. Anatomic-roentgenographic study of structures visualized 5 cm. above baseline plane.

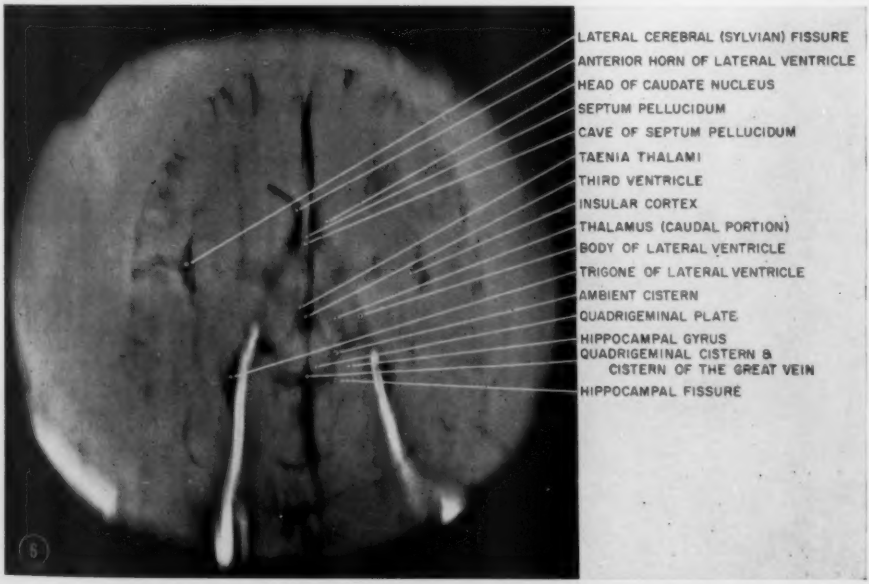

FIG. 6. Anatomic-roentgenographic study of structures visualized 6 cm. above baseline plane.

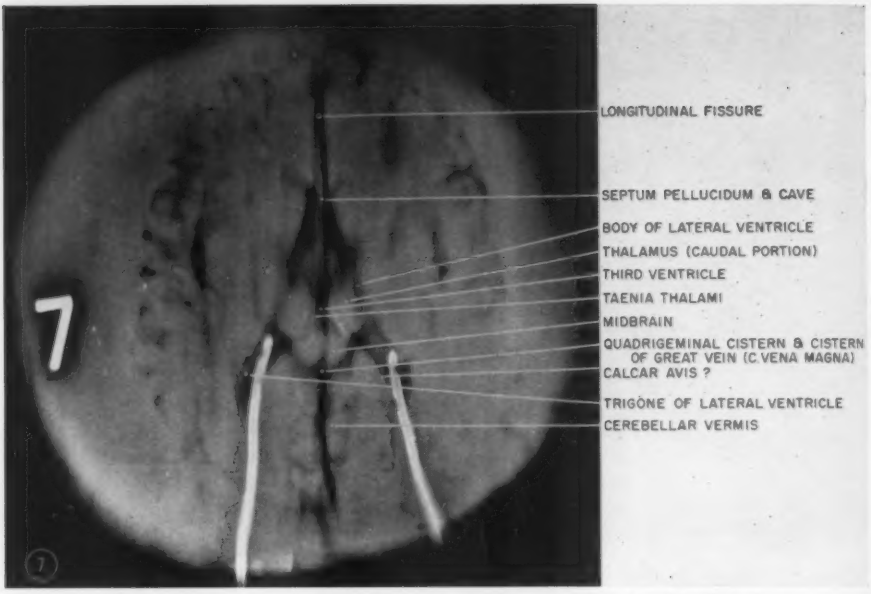

FIG. 7. Anatomic-roentgenographic study of structures visualized 7 cm. above baseline plane.

The authors wish to acknowledge the helpful editing of the anatomic interpretations by Professors W. Ross Adey and H. W. Magoun of the department of anatomy, University of California Medical Center.

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Localized cerebral hypoglycemia simulating stroke

A clinical and experimental study

John S. Meyer, M.D. and Harold D. Portnoy, M.D.

IT IS COMMON NEUROLOGIC EXPERIENCE that the signs of hypoglycemia consist of slow speech, clouding of consciousness, disorientation, impaired memory, and release of grasp and sucking reflexes. If hypoglycemia continues, these signs of cortical impairment are followed by coma, constricted pupils, respiratory irregularity, and, finally, circulatory collapse.[1] If glucose is administered promptly before respiratory and circulatory failure occur, there is rapid recovery from the disability.

At various times, unusual cases have been reported in which signs of localized neurologic impairment appear to have been caused by hypoglycemia and alleviated by the administration of glucose.[2–4] Such unusual neurologic signs may occur with hypoglycemia caused by excessive dosage of insulin in the treatment of diabetes or as a complication of insulin-producing tumors.[5–7] In the cases cited, signs such as hemiplegia, hemianesthesia, dysphasia, diplopia, nystagmus, and dysarthria appeared during hypoglycemia and often simulated occlusion of a major cerebral vessel. In a recent review of 91 cases of hyperinsulinism, four were diagnosed as "cerebrovascular accident" before correct diagnosis was established.[8]

It is the purpose of this report to summarize clinical observations in five additional cases of hypoglycemia associated with localized neurologic deficit and to present the results of an experimental study designed to clarify the nature of their cause. The subject is of importance because failure to recognize and treat hypoglycemia commonly results in permanent neurologic deficit or death.

CLINICAL OBSERVATIONS

Case 1. A 74 year old woman was brought to the emergency room of the Detroit Receiving Hospital on December 13, 1957 with the diagnosis of "stroke," since the patient had been found unresponsive and paralyzed. The patient was well-known to the medical staff, since she had had five previous admissions for control of diabetes which had been present for 20 years. Her dose of NPH insulin had been 46 units daily.

On examination the following positive physical signs were found. Blood pressure was 140/50, pulse 70 per minute and regular, temperature 99° F., and respirations stertorous. The medical examination was unremarkable except for the neurologic disorder. Her speech was severely dysarthric and unintelligible. There was profuse salivation and the skin was cool and moist. A Horner's syndrome was present on the left, associated with a paralysis of conjugate gaze to the same side; in addition, there was a central type of facial weakness on the left. All four limbs were weak and spastic. Tendon jerks were symmetrically hyperactive and a Babinski sign was present in both lower extremities. There was no response to pinprick below the neck, but there was grimacing when she was stimulated on the face with a pin. Blood sugar was reported as 48 mg. per cent. The hypoglycemia was treated by the slow intravenous injection of 50 cc. of 50 per cent aqueous glucose solution. During the injection there was partial return of motor movement in all four limbs but, although speech became comprehensible, there was persistent dysarthria. She improved steadily and four hours later she was speaking normally. Examination at this time showed that she was fully oriented but that her judgment was impaired. She was euphoric; there was amnesia for the episode and a tendency to pathologic

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laughing and crying. Visual fields were normal. There was minimal weakness of movement of the left face, slight ataxia of gait, and terminal tremor on finger-to-nose testing, with incoordination of the lower limbs on heel-to-shin testing. Motor strength was normal. A grasp reflex was present bilaterally. The deep tendon reflexes were less active than on admission and the right plantar reflex was abnormal. Pain sensation was present but diminished below the eighth thoracic dermatome bilaterally. Brief compression of each carotid artery in the neck produced no effect. There were no abnormal neurologic signs on re-examination 24 hours later.

Lumbar puncture showed an initial pressure of 175 mm. of water. The cerebrospinal fluid was crystal clear. There were no cells present in the fluid and the Kline, Pandy, and colloidal gold tests were negative. The cerebrospinal fluid sugar was 49 mg. per cent, the total protein 36 mg. per cent, and the chlorides 127 mEq. per liter. Electroencephalogram showed a basic pattern of moderate amplitude alpha activity, with frequent bursts of high amplitude slowing in the theta and delta range asymmetrically localized in both occipital and posterior temporal regions (figure 1A). Repeat electroencephalogram three weeks later showed no abnormality (figure 1B).

The clinical diagnosis was basilar artery insufficiency precipitated by hypoglycemia, with hypoglycemic symptoms predominantly referable to the upper brainstem and cerebellum. For the first 24 hours she was treated with glucose; thereafter her blood sugar was controlled between 190 to 240 mg. per 100 cc. of blood. At the time of discharge four weeks later, the insulin dose had been reduced to 30 units. There have been no further attacks.

Because of the unusual nature of this disorder and the importance of confirming the diagnosis in order to prevent further attacks, the problem was discussed with the patient and she agreed to undergo carefully controlled hypoglycemia while under observation in hospital. The electroencephalogram was recorded while hypoglycemia was induced (figure 1). After the patient had remained asymptomatic for three weeks, regular insulin was administered in repeated doses of 20 units until the blood sugar was reduced to 40 mg. per 100 cc. of blood. At this point moderate symptoms comparable to those present on admission were reproduced. The attack was then terminated by the injection of 25 gm. of glucose intravenously, followed by a continuous slow infusion of an additional 150 gm. over the ensuing eight hours. During the induction of hypoglycemia, the patient was examined repeatedly. The first change was euphoria, followed by inappropriate laughter and dysarthria of the cerebellar type. At this time the electroencephalogram showed slow activity in the occipital and posterior temporal regions (figure 1 C and D). Vertical and rotatory nystagmus then appeared, with weakness of the left side of the face and inability to count or solve simple problems. The electroencephalogram showed changes similar to those present on admission (figure 1E and F). Following this, the patient became flushed with diaphoresis and the electroencephalogram showed occipital, parietal, and temporal delta activity (figure 1G). The attack was terminated by glucose injected intravenously, and the neurologic examination and electroencephalogram rapidly returned to normal (figure 1H). There was amnesia for the test.

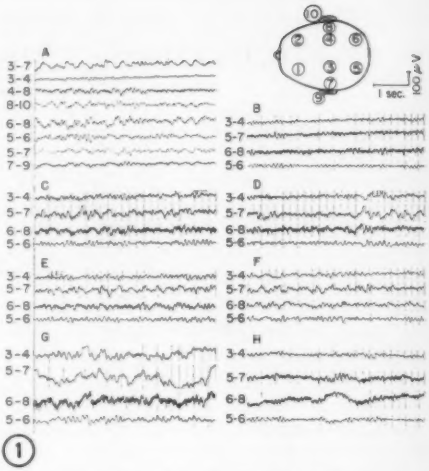

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FIG. 1. Samples of electroencephalographic records from *case 1*, a 74 year old diabetic woman with basilar artery insufficiency and signs of brainstem paralysis precipitated by hypoglycemia. *A.* Record made at the time of admission when patient was semistuporous and dysarthric, with left gaze palsy, left facial weakness, and quadriparesis. Slow waves were present in both posterior temporal and occipital regions. Blood sugar was 40 mg. per cent. *B.* Record made three weeks after recovery brought about by administration of glucose. Blood sugar was 198 mg. per cent. *C.* Record made two hours after repeated doses of regular insulin (total 180 units). Occipitotemporal slowing is appearing. *D.* Record 30 minutes later. At this time neurologic examination revealed pathologic laughing, release of the grasp reflex, dysarthria, and disorientation. *E.* Fifteen minutes later, there was lateral nystagmus and she was unable to solve simple problems. Occipitotemporal slowing was more marked in the electroencephalogram. *F.* Ten minutes later, there was vertical nystagmus and she was obtunded and dysarthric. *G.* Five minutes later, blood sugar was 40 mg. per cent. She was flushed and sweating. Electroencephalogram was similar to record *A.* Twenty-five gm. of glucose injected intravenously. *H.* Ten minutes after glucose injection. She was asymptomatic; electroencephalogram was normal other than perspiration artifact.

Case 2. A 38 year old taxi-driver was admitted to the neurology service of Dearborn Veteran's Hospital on March 1, 1958 in stupor, with weakness of the left extremities. For three years he had suffered from episodes of unconsciousness, preceded by numbness of the body and tempo-

rary blindness. He had found that these symptoms were improved by ingesting sugar. Two electroencephalograms made two years prior to admission were found to be normal. One month before admission an episode of loss of consciousness resulted in an automobile accident. On the day prior to admission he became confused, unable to recognize friends and relatives, complained of diplopia and blurred vision, and crawled around his house on all fours. He then fell asleep and was difficult to arouse. The family noted his left arm and leg had become weak.

On physical examination the temperature was 99° F., pulse 90, and blood pressure 110/70. His general medical examination revealed no abnormality. He varied from coma to stupor, and there were frequent episodes of decerebrate rigidity, with Cheyne-Stokes respiration. The pupils were small, equal, and reacted to light, but both eyes were constantly deviated to the right. The fundi were natural. The corneal reflexes were absent, all reflexes were hyperactive, and a Babinski sign was elicited in both lower extremities.

Lumbar puncture produced clear spinal fluid with an initial pressure of 170 mm. of water and a final pressure of 130 mm. of water. There were no cells present, the Pandy test was negative, the total protein was 38 mg. per cent, and the sugar was 48 mg. per cent. Roentgenograms of skull and spine were negative, and carotid arteriograms showed no abnormality of the internal carotid and middle cerebral arteries.

After administration of intravenous glucose, the patient responded gradually and within 24 hours he was fully oriented. At this time bilateral nystagmus was noted. The visual fields were normal, but there was hypesthesia and hypalgesia of the left side of the face. The gait was grossly ataxic and there was spasticity of the left leg. Cerebellar incoordination was greater in the left hand than the right. The jaw jerk was hyperactive and all tendon reflexes were increased in the left limbs. The left plantar reflex was extensor, the right was flexor. Sensation over limbs and trunk was normal. These signs gradually subsided over the next three days. Daily fasting blood sugar values were consistently low and ranged from 34 to 53 mg. per cent. An intravenous glucose tolerance test with 25 gm. of glucose showed an abnormally rapid utilization of glucose. The blood sugar rose from 72 mg. per cent to 120 mg. at the first hour, fell to 98 mg. the second hour, 107 mg. the third hour, 73 mg. the fourth hour, 53 mg. the fifth hour, and 83 mg. the sixth hour.

The patient was fasted for 42 hours and the test was terminated when his blood sugar fell to 15 mg. per cent and he became weak and drowsy. He was then placed on a low carbohydrate diet; the second day he became confused, disoriented, and diaphoretic, with nystagmus on lateral gaze. His blood sugar was found to be 8 mg. per cent. Intravenous injection of 25 gm. of glucose resulted in immediate recovery. The upper gastrointestinal tract was studied roentgenographically after ingestion of barium and the duodenal loop appeared normal. On April 12 an exploratory laparotomy was performed and the body and tail of the pancreas were excised, together with the spleen. There was a 1.5 cm. cystic tumor of the neck of the pancreas and several firm nodules in the body and tail of 0.5 to 1.5 cm. in size. On microscopic examination these nodules proved to be adenomata of the islets of Langerhans. The preoperative diagnosis of islet cell tumor of the pancreas, with localized neurologic disorder due to hypoglycemia, was thus confirmed at operation. It is of special interest that the reversible nature of the neurologic disorder led us first to suspect the diganosis of hyperinsulinism. He has had no further neurologic symptoms since operation.

Case 3. A 25 year old male diabetic was admitted to the Newton-Wellesley Hospital, Newton, Massachusetts, in 1955 because of drowsiness and inability to talk. He had been taking 48 units of NPH insulin daily, but on the day of admission he took an excessive dose by error. He had felt drowsy and weak all day and was unable to eat. He was brought to the hospital because he had lost his ability to speak.

Glycosuria had been first noted at the age of four and he had been taking insulin daily since that time; he had often suffered from "insulin reactions." There was no history of cardiovascular disease or previous neurologic complaint.

On physical examination the blood pressure was 120/80, pulse was regular at 80 per minute, and respirations were regular at 18 per minute. There were no abnormalities upon physical examination of the heart, lungs, and abdomen. The patient was pale, apprehensive, and was sweating profusely.

A total motor aphasia was present; however, he was able to shake or nod his head in answer to simple questions. The ocular fundi were normal. There was a paresis of the right third nerve, with ptosis and an enlarged pupil which responded sluggishly to light. Sensation was intact over the face and the corneal reflexes were intact. There was a central type of right facial weakness, but the other cranial nerves were intact. Tone was increased in the right limbs, with slight weakness of the right hand grip. The deep tendon reflexes were increased on the right and a Babinski sign was present on the right. Sensation was intact.

Prior to neurologic consultation by one of the authors, the diagnosis was cerebral thrombosis. Forty cc. of 50 per cent glucose was injected intravenously; within a few minutes the patient was talking normally and neurologic examination showed no deficit. Four hours later he again became pale, sweaty, drowsy, and unable to talk. Glucose was again given intravenously; within two minutes he was able to talk. Four hours after the second episode, a blood sugar was drawn for the first time and was found to be 60 mg. per 100 ml. of blood. Detailed blood counts, urinalyses, and blood chemistry examinations including serum electrolytes were normal. Lumbar punc-

ture performed eight hours after admission showed crystal clear cerebrospinal fluid, with an initial pressure of 140 mm. of water. There were ten erythrocytes and one lymphocyte per cc. of fluid, the total protein was 26 mg. per cent, and the sugar was 42 mg. per cent. The insulin dose was reduced to 30 units NPH insulin daily, resulting in elevated blood sugar levels ranging between 300 and 365 mg. per cent.

On this regimen there have been no further neurologic complaints.

Case 4. A 36 year old diabetic physician was brought to the hospital because of loss of speech and weakness of the right side. His wife thought he had had a "stroke." For eight years he had suffered from diabetes, for which he took 60 units of NPH insulin daily. He had rarely experienced mild insulin reactions and usually maintained a well-regulated diet of 2,500 calories per day. The day before admission he had driven his car for many hours, missed his lunch, and had eaten a light supper. At 5:00 a.m. he awakened his wife, who found him unable to speak, with dilated pupils and sweating profusely. He had a generalized seizure before she was able to bring him to hospital by ambulance.

On examination blood pressure was 130/70, pulse 70 and regular, and respirations 16 per minute. The patient was agitated and anxious because of a total inability to speak. He understood and obeyed simple commands, however, and cooperated in performing the neurologic examination. The general medical examination revealed no abnormalitiy. The pupils were both 5 mm. in diameter and reacted briskly to light. The visual fields and fundi were unremarkable. Other cranial nerves were normal. There was slight weakness of the right hand grip and the deep tendon reflexes were decreasd in the right arm and leg. A Babinski sign was present on the right side. There was no sensory disturbance. The blood sugar was 50 mg. per cent. Routine laboratory examinations were normal. A lumbar puncture was not performed.

Ten per cent glucose was given by intravenous infusion; within a few minutes speech returned, although a marked motor dysphasia persisted for 15 minutes. He was advised to reduce his insulin dosage to 50 units of NPH insulin daily, with instructions to avoid fasting and exhaustion. He made an uneventful recovery. At the time of discharge he was without neurologic deficit.

Case 5. A 53 year old woman was admitted to hospital because of status epilepticus partialis continua. Twelve months previously a total gastric and pancreatic resection had been performed for carcinoma of the head of the pancreas. In an attempt to control steatorrhea and diarrhea postoperatively, a high carbohydrate diet was prescribed, together with 20 units of NPH insulin daily. Without medical advice, the patient increased her dose of insulin to 40 units of NPH insulin daily. Three weeks prior to admission she had an insulin reaction, with sweating, weakness, irritability, and confusion; these symptoms improved promptly after injection of glucose. On the day of admission she had a similar attack and her husband gave her an injection of an additional 10 units of insulin prior to calling her physician.

On examination the patient was a cachectic woman having frequent seizures. With each seizure, she abruptly ceased to respond, the head and eyes rotated to the right, and myoclonic twitching began in the right face and then spread to the right hand, arm, and leg. After two or three minutes the convulsions would cease, partial consciousness would be regained, and she would be able to converse before another seizure occurred. The blood pressure was 100/55, and the pulse and respirations were regular. The tongue was smooth and red. The chest and heart were normal, except for slight emphysema. The abdomen was moderately distended and tympanitic, with a healed surgical scar and atrophy of the skin. No masses were palpable.

On neurologic examination there was disorientation, lack of cooperation, and irritability between seizures. The visual fields were normal, there was no papilledema, and the pupils were of equal size and reacted promptly to light. Eye movements were normal except during seizures. There was a central type of right facial weakness and a moderate degree of spastic hemiparesis on the right. The deep tendon reflexes were increased on the right and a Babinski sign was present on the right. There was a sucking reflex and forced groping and grasping of the right hand. There was no loss of sensation.

Treatment consisted of the intravenous infusion of 10 per cent glucose and intragastric feeding with a high carbohydrate diet. The seizures decreased in frequency over the ensuing 24 hours and she became more responsive. Dilantin, 100 mg. three times daily, was instituted, together with a single intravenous infusion of 100 mg. of sodium phenobarbital. The seizures ceased on the second day. Gradual recovery from the right hemiparesis occurred over the next two days. The patient was discharged without neurologic signs three weeks later. She was taking a high carbohydrate diet and 10 to 15 units of insulin daily. With this regimen, a slight glycosuria was maintained purposely.

During her illness extensive laboratory studies were performed which will be summarized briefly. Complete blood count was within normal limits. Roentgenograms of chest and skull revealed no abnormalities. Lumbar puncture showed crystal clear cerebrospinal fluid without abnormality of cell count, total protein, serologic test for syphilis, or colloidal gold reaction. Unfortunately, a blood sugar was not drawn prior to glucose therapy, but the history and response to glucose were sufficiently distinctive to permit a clinical diagnosis of hypoglycemia with focal epilepsy and hemiparesis.

In all five of these cases, we were impressed by the severity of the localized disorder that

may accompany hypoglycemia and considered it of sufficient importance to investigate the nature of its pathogenesis in experimental animals. The method of experimental study, together with our results, will be described.

EXPERIMENTAL METHODS

Experiments on animals were designed to test the hypothesis that hypoglycemia first produces failure of neuronal supply of glucose in an area of tenuous blood supply (such as may result from atherosclerosis or vascular maldevelopment in man or from occlusion of cerebral vessels in animals) resulting in a localized neurologic deficit.

To test this hypothesis, acute and chronic experiments were performed in seven cats and eight monkeys (Macacus rhesus and cynomologous). Since the purpose of the acute and chronic experiments was slightly different, they will be described separately.

CHRONIC EXPERIMENTS

In one cat and eight monkeys the middle cerebral artery was occluded, using aseptic technic, after reflecting an osteoplastic bone flap and inserting a sterile window in the skull.[9,10,11] Establishment of collateral blood flow was aided by preventing a fall in blood pressure and by the use of heparin.[9] These animals showed little, if any, functional deficit seven to ten days following occlusion of the middle cerebral artery, but had been shown previously to be subject to transient hemiplegia by any stimulus which tends to upset the precarious balance between circulatory supply and local metabolic demand.[10] Seven to 70 days after occlusion of the middle cerebral artery, the animals were subjected to insulin hypoglycemia. They were examined repeatedly for signs of any functional deficit, the pial vessels were observed, and the blood pressure was recorded frequently. In all animals 16 mm. motion pictures were made before, during, and after insulin hypoglycemia. The systolic blood pressure was recorded by means of a pediatric sphygmomanometer cuff placed around the lower abdomen.[10] In representative animals blood sugar determinations were made before and after the appearance of hypoglycemic signs. Hypoglycemia was terminated by the intravenous injection of 20 cc. of 50 per cent glucose, supplemented in later experiments by oral glucose, since recurrent hypoglycemia was common if oral supplement was not given. In the same animals repeated hypoglycemic episodes were induced, using varying doses of insulin, and in a few instances NPH insulin was compared with the effects of regular insulin. Comparison was made of administration of insulin in the fasting and non-fasting state. In four chronic experiments 8 to 16 cc. of filtered Trypan blue was injected intravenously before and after insulin hypoglycemia to observe any evidence of endothelial damage.[12]

ACUTE EXPERIMENTS

In six cats the middle cerebral artery was occluded near its origin from the circle of Willis during light Nembutal (0.5 mg. per kg.) and atropine (0.05 to 0.1 mg. per kg.) anesthesia. Four large pial arterioles were occluded, in addition. After collateral blood flow was established, experiments were then performed in order to compare local oxygen consumption, blood flow, and electroencephalogram in the territory of supply of the occluded vessel, with concurrent measurements made from the intact hemisphere. In no experiment was there cortical infarction, as judged by observation of the continuing circulation with a dissecting microscope.

Measurements of cerebral oxygen tension, cortical temperature, electroencephalogram, and direct femoral blood pressure were recorded with an eight-channel Offner ink-writing oscillograph, four channels of which were modified for direct current recording by use of type 9138 input couplers.[13,14,15] Cortical and subcortical oxygen tension was recorded by the polarographic method, using open-tip platinum cathodes insulated with teflon. Since our main concern was with relative readings, absolute values of oxygen tension were not determined accurately. Changes in cortical blood flow were monitored with microthermistors inserted into the cortex. The electroencephalogram was recorded, using bipolar technic from platinum needles inserted into the skull or placed on the dura. The validity of these methods has been discussed in a previous paper.[16] In addition, the pial circulation was observed with a dissecting microscope.

The lateral portions of each hemisphere were exposed and the middle cerebral artery was occluded on one side only. The collateral circulation was maintained by preventing reduction in blood pressure and by the use of heparin. Electrodes were placed symmetrically on each hemisphere in order to sample the territory supplied by both the normal and occluded vessel, so that the records made from the normal hemisphere could be used for purposes of control. Records were then made of the effects of brief nitrogen breathing and occlusion of the common carotid arteries by traction on loose ligatures placed around them before and after hypoglycemia. Under such circumstances, the gradient of fall in oxygen tension depends on the rate of local metabolic oxygen consumption, providing the respiratory rate and blood pressure are not altered.[13] By this means the metabolic rate of oxygen of the two hemispheres could be compared before and after hypoglycemia.

Several comparable records of the effect of nitrogen breathing and occlusion of the common carotid arteries were obtained in the steady state and the blood sugar was determined. Insulin was then injected and tests of nitrogen breathing or carotid occlusion were repeated at intervals of 15 minutes. When suitable records had been made during hypoglycemia, 5 to 7.5 gm. of glucose were injected intravenously and the tests were repeated at intervals after the blood sugar had been restored.

NEUROPATHOLOGIC STUDIES

All animals except two were sacrificed in the absence of shock or respiratory embarrassment. The brain was fixed in situ by intracardiac perfusion with 10 per cent formalin and saline. Following fixation, each hemisphere was embedded in paraffin and comparable sections of the "control" and "ischemic" hemispheres were stained by hematoxylin and eosin and Nissl stains.

EXPERIMENTAL RESULTS

Hypoglycemic hemiplegia. In all chronic experiments (in which recovery had occurred following occlusion of the right middle cerebral artery), hypoglycemia produced further impairment of function in the limbs opposite the occluded vessel. In the cat this consisted of hemiparesis, unilateral loss of hopping and placing reactions (figure 2), and loss of righting reactions on the affected side. This began 35 minutes after the injection of 15 units of insulin and was maximum after one hour. In the monkey the deficit was much more severe and predictable. Beginning 30 minutes after injection of regular insulin and progressing during the next 30 to 45 minutes, weakness and incoordination appeared first in the use of the left forelimb (figure 3B and C). This was followed by weakness of the left side of the face and pinprick caused no reaction over the left face and forelimb. The phenomenon of "levitation" then appeared in the left forelimb.[17] In slightly less than one-half of the inductions of hypoglycemia, seizures occurred at the onset of hemiparesis and were almost always localized to the paralyzed side. Usually these consisted of jacksonian seizures progressing from one side of face and tongue to the homolateral arm and leg. Usually they subsided spontaneously within ten minutes and were followed by hemiplegia. Maximal symptoms occurred one to one and a half hours after injection of regular insulin and three to four hours after NPH insulin. These symptoms

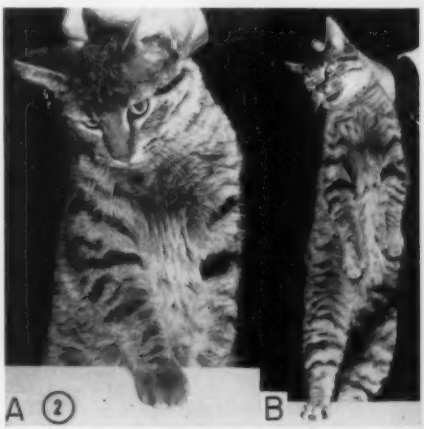

FIG. 2. Hemiparesis in the cat produced by insulin hypoglycemia. The animal had fully recovered from occlusion of the right middle cerebral artery four weeks previously. *A.* Absence of placing reaction in left forepaw two hours after the intramuscular injection of ten units of regular insulin. *B.* Absence of placing reaction in left hindpaw. Hopping and righting reflexes were also lost on the left. Administration of oral glucose resulted in rapid restoration of these reflexes.

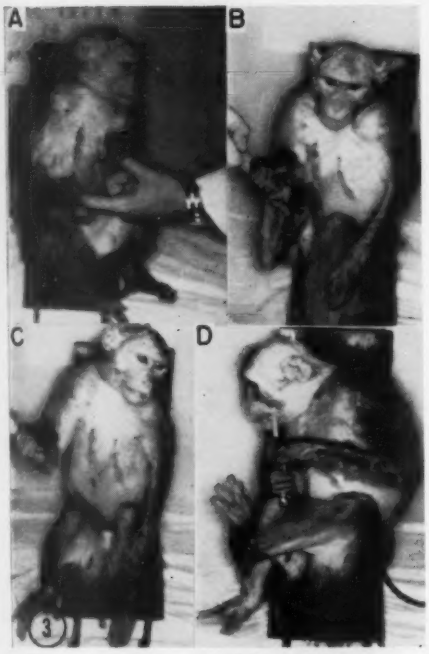

FIG. 3. Production of transient hemiplegia in the macacus rhesus monkey by insulin hypoglycemia and recovery by administration of glucose. *A.* Two weeks after occlusion of the right middle cerebral artery, the animal shows no neurologic deficit. Systolic blood pressure is 106 mm. of mercury. Pial vessels appear normal, as viewed through window in skull. *B.* Forty minutes after 25 units of regular insulin, left hemiplegia is present and pial venules in ischemic area are orange-red. *C.* Two hours after insulin, the hemiplegia still persists. Blood pressure is 120 mm. of mercury. *D.* Five minutes after 5 gm. of glucose administered intravenously, strength and coordination of the left limbs are normal. Eight cc. of Trypan blue injected intravenously during hemiplegia did not produce perivascular staining of pial vessels viewed through the window.

consisted of homonymous hemianopia (absent blink response to visual threat in the half-field), tonic deviation of head and eyes away from the paralyzed side, flaccid hemiplegia, and unilateral absence of response to painful stimulation, with depressed or absent tendon jerks on the affected side (figures 4B and 5B). Administration of intravenous glucose produced improvement within 20 seconds of injection, and recovery from hemiplegia was usually complete within 10 to 20 minutes (figure 3D). During episodes of hypoglycemic hemiplegia, the blood pressure remained unchanged or became slightly elevated, pial venules in the area of ischemia showed a change in color from blue to red, but blood flow appeared unchanged. The oxygen tension of cortex did not alter significantly in one experiment, and intravenous injection of Trypan blue failed to show evidence of endothelial damage. In non-fasting animals the dose of insulin required to produce symptoms was frequently as high as 100 units or more, although in the fasting state 25 units regularly produced severe signs. In three animals the blood sugar values during symptoms varied between 4.2 and 9 mg. per cent.

Protracted hemiplegia due to insulin shock with hemodynamic crisis. In two animals given excessive doses of insulin in whom there was a fall in blood pressure associated with severe delayed hypoglycemia occurring several hours after administration of insufficient glucose, the intravenous injection of further glucose produced only partial recovery from hemiplegia and full recovery was delayed for several days. In one of these animals perivenular hemorrhages were seen to develop through the skull window, following restoration of blood pressure with additional glucose therapy. Providing there was no fall in blood pressure, as many as 15 attacks of hypoglycemic hemiplegia were produced in the same animal with a surprising degree of recovery, although some permanent hemiparesis eventually persisted.

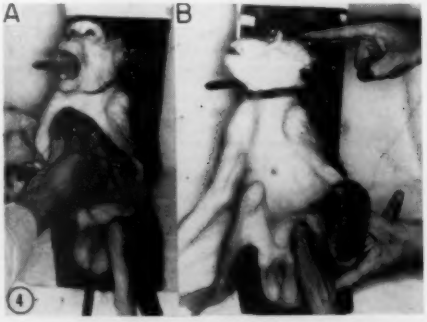

FIG. 4. Production of transient hemiplegia in cynomologous monkey by hypoglycemia. *A.* Sixty-three days after occlusion of the middle cerebral artery, the animal shows no neurologic defict (fasting blood sugar 70 mg. per cent). *B.* Two hours after 20 units of regular insulin, there is flaccid hemiplegia and hemianopia on the left; the head and eyes are deviated to the right (blood sugar 4.2 mg. per cent).

FIG. 5. Photographs to show production of transient hemiplegia in a cynomologous monkey nine days after recovery from occlusion of the right middle cerebral artery by the intramuscular injection of 20 units of regular insulin. *A.* Fasting animal prior to insulin to show normal strength in all four extremities. *B.* Forty-five minutes after insulin, hemiplegia is present.

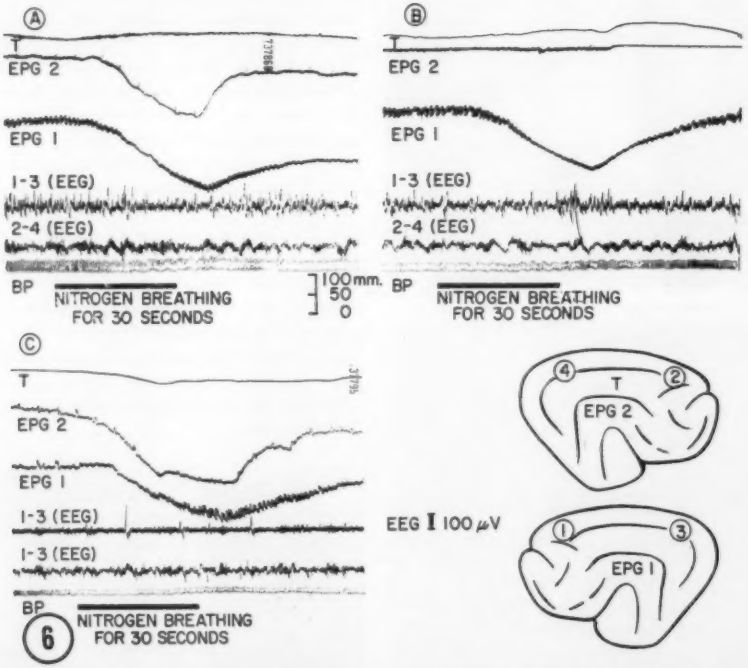

FIG. 6. Samples of record from the same experiment in a cat recovered from occlusion of the right middle cerebral artery to show the reduction of oxygen consumption of cerebral cortex in the ischemic area resulting from hypoglycemia and its restoration to normal by administration of glucose. *A.* Concurrent records of cortical temperature (T), electroencephalogram (1-3, 2-4), and oxygen tension (EPG 2) recorded from the right hemisphere of the fasting cat prior to insulin. EPG I is a record made from the left (intact) hemisphere for purposes of control. Brief nitrogen breathing produces a steep gradient of fall in oxygen tension recorded from both hemispheres. The cortical temperature shows slight rise. *B.* Thirty-five minutes after 20 units of regular insulin, there is little, if any, reduction in cortical oxygen tension (EPG 2) recorded from the ischemic area with nitrogen breathing and a slight reduction in gradient of fall in the left hemisphere. The cortical temperature still shows a slight rise. *C.* Twenty minutes after 5 gm. of glucose, nitrogen breathing again produces a reduction of cortical oxygen tension similar to control record (*A*). The lower electroencephalogram (labeled 1-3 instead of 2-4) shows less slow activity than during hypoglycemia. Position of electrodes shown on brain diagrams. Lowest trace is blood pressure (B.P.) recorded from femoral artery. B.P. calibration shown in lower right corner of *A*. Calibration of electroencephalogram shown to left of brain diagrams. Time calibration is indicated by black line showing length of nitrogen breathing.

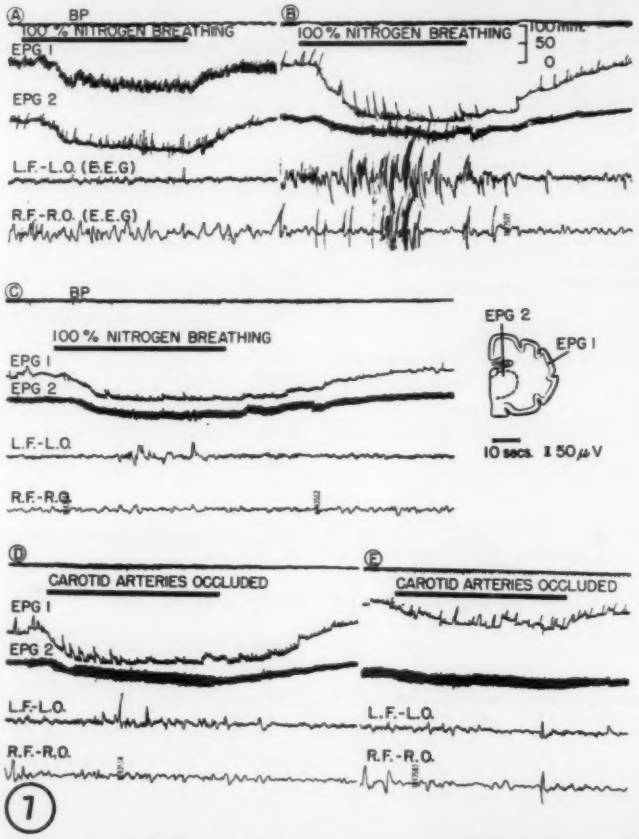

FIG. 7. Samples of records from the same experiment in a cat (recovered from occlusion of the left middle cerebral artery) to show reduction of cortical and subcortical oxygen consumption in the ischemic area resulting from hypoglycemia. *A.* Concurrent records of blood pressure (B.P.), electroencephalogram from left (L.F.-L.O.) and right (R.F.-R.O.) fronto-occipital cortex, and cortical (EPG 1) and thalamic (EPG 2) oxygen tension in the distribution of the occluded vessel. Brief nitrogen breathing produces a steep gradient of fall in oxygen tension recorded from both cortex and thalamus. Blood sugar is 120 mg. per cent. *B.* Thirty-five minutes after injection of 30 units of regular insulin intravenously. Cortical spike activity is present in the electroencephalogram of both hemispheres, more marked on the left. The gradient of fall in thalamic oxygen tension with nitrogen breathing is reduced, but that of the cortex is steeper and much greater due to increased oxygen metabolism with cortical seizure activity. *C.* Forty-five minutes after insulin, seizure activity has subsided and cortex and thalamus now show a less steep gradient of fall in oxygen tension with nitrogen breathing. *D.* Twenty minutes after insulin, the fall in cortical and thalamic oxygen tension with brief occlusion of both carotid arteries is not altered. *E.* Fifty-five minutes after insulin, brief occlusion of both carotid arteries produces a less steep fall in both cortical and thalamic oxygen tension. Blood sugar is 8.4 mg. per cent. Position of EPG electrodes in left hemisphere shown in brain diagram. Calibration of femoral blood pressure is shown in *B.* Time and electroencephalogram calibrations are shown below brain diagram. In the course of experiment some 60 cycles per second alternating current artifact appeared in the record of EPG 2, but the electrode continued to respond to changes in oxygen tension.

Acute experiments. In these experiments (in which every effort was made to maintain an excellent collateral circulation) cortical temperature, electroencephalogram, and oxygen consumption in the ischemic territory rapidly became restored to normal.[9,11,12] One hour after occlusion of the middle cerebral artery, the gradient and degree of reduction of cortical oxygen tension produced in the ischemic area by brief nitrogen breathing were compara-

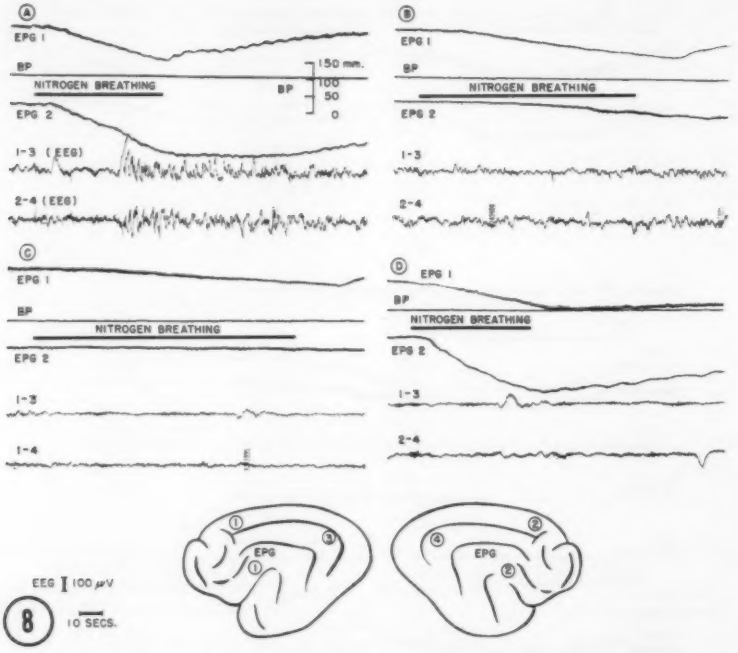

FIG. 8. Samples of record from the same experiment in a cat that had recovered from ligation of the right middle cerebral artery. *A*. Fasting animal to show concurrent records of femoral blood pressure (B.P.), cortical oxygen tension (EPG), and electroencephalogram of each hemisphere. During brief nitrogen breathing, there is steep fall in oxygen tension of both hemispheres (blood sugar 100 mg. per cent). *B*. Forty-five minutes after 80 units of regular insulin, the gradient of fall in cortical oxygen tension with a longer period of nitrogen breathing is less steep in records from both hemispheres, but the change is greater in the ischemic hemisphere. *C*. Two hours after insulin, there is minimal change in EPG 2 with prolonged nitrogen breathing and the gradient of fall in oxygen tension recorded by EPG 1 is also further reduced. Occlusion of both carotid arteries at this time was similar to effect of nitrogen breathing (blood sugar 5.2 mg. per cent). *D*. Twenty minutes after 4 gm. of glucose intravenously, the cortical oxygen consumption demonstrated by brief nitrogen breathing is similar to the record *A* prior to insulin. Respirations were constant at 28 per minute during all records. Position of electrodes shown in brain diagrams. Calibration of femoral blood pressure shown in *A* of time and electroencephalogram to left of brain diagrams.

ble to that obtained from the normal hemisphere (figures 6A, 7A, 8A, and 9A). Thirty to 45 minutes after the injection of insulin in the fasting animal, the earliest changes began and were well established within 90 minutes (figures 6B, 7C, 8B and C, and 9B). There was no significant change in the cortical temperature (figures 6 and 9) or blood flow in the pial vessels observed with the microscope during hypoglycemia. However, the pial venules, particularly in the ischemic region, showed a progressive change in color from blue to orange-red during hypoglycemia. In addition, the electroencephalogram during hypoglycemia showed a varying degree of slowing and reduction in amplitude of fast activity which was usually more marked in the ischemic hemisphere (figures 6B and C, and 7C and E). Spike activity appeared during hypoglycemia in three animals; it was localized to the ischemic area in two and was diffuse in one (figure 7). The spike activity usually appeared within 30 minutes of insulin injection and seldom persisted for longer than 15 minutes, but occasionally reappeared after glucose injection.

Provided spike activity did not appear in the electroencephalogram, a progressive flattening of the gradient and degree of fall in cortical and subcortical oxygen tension with

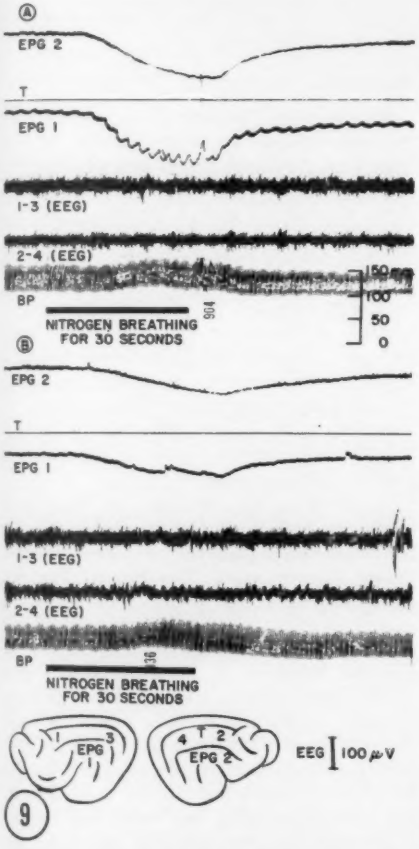

FIG. 9. Samples of record from the same experiment in a cat in whom the right common carotid artery had been ligated. Because of the excellent collateral circulation in the cat, there was no significant difference between the fall in cortical oxygen tension with nitrogen breathing from either hemisphere during hypoglycemia, although both showed a less steep gradient of fall. *A*. Concurrent records of femoral blood pressure (B.P.), cortical oxygen tension (EPG), temperature (T), and electroencephalogram during brief nitrogen breathing prior to insulin (blood sugar 90 mg. per cent). *B*. Fifty minutes after 35 units of regular insulin. The gradient of fall in oxygen tension from both hemispheres is comparably reduced (blood sugar 4.0 mg. per cent). Position of electrodes shown in brain diagrams. Calibration of femoral blood pressure, which was unusually high is shown in *A*. Calibration of electroencephalogram is to right of brain diagram and time calibration is indicated by the black line showing length of nitrogen breathing.

nitrogen breathing appeared 30 to 45 minutes after injection of insulin and was well marked after one to one and a half hours. This depression of the cerebral metabolic rate of oxygen always appeared in the ischemic territory first and was always greater in that region (figures 6B, 7C, and 8B and C).

In the cat occlusion of one common carotid artery (which fails to produce significant ischemia because of a rich collateral circulation) did not significantly alter the response to nitrogen breathing during hypoglycemia recorded by an oxygen electrode placed in its territory of supply (figure 9B). In all animals in which the middle cerebral artery had been occluded, however, hypoglycemia regularly produced a flattening of the gradient of oxygen consumption, appearing first in the distribution of the occluded vessel. A less steep gradient of fall in oxygen tension in the distribution of the occluded vessel could also be demonstrated by temporary occlusion of the carotid arteries in the neck (figures 7D and E). The intravenous injection of 5 to 7.5 gm. of glucose promptly restored a steep gradient of fall in oxygen tension, with nitrogen breathing comparable to that recorded prior to administration of glucose (figures 6C and 8D). If hypoglycemia was not terminated one to two hours after injection, there was progressive flattening of the gradient of fall of oxygen tension in the intact hemisphere also.

In five animals in which blood sugar de-

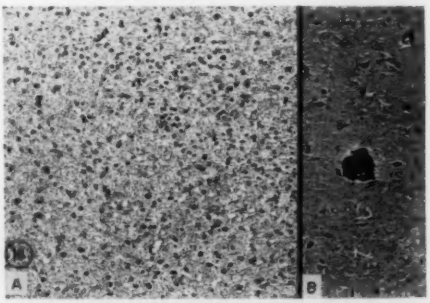

FIG. 10. *A*. Photomicrograph of the parietal cortex of a monkey in the distribution of the middle cerebral artery which had been occluded 19 days before. This animal had been subjected to hypoglycemia for two to six hours daily for five days prior to sacrifice. There is recent necrosis of nerve cells. Hematoxylin and eosin stain. *B*. Photomicrograph of the ectosylvian cortex of a cat to show perivascular and pericapillary hemorrhages in the distribution of the occluded middle cerebral artery produced by severe hypoglycemic shock with fall in blood pressure. The duration of hypoglycemic shock was eight hours. Hematoxylin and eosin stain.

terminations were made, the pre-insulin values were 70 to 120 mg. per 100 cc. of blood and the values after insulin were 4.2 to 10 mg. per 100 cc. of blood. Fasting animals with a blood sugar of 70 to 90 mg. per 100 cc. required smaller doses of insulin (15 to 25 units) to produce the effect described than non-fasting animals who required doses of 25 to 40 units.

Neuropathologic changes. The brain was examined histologically in all experiments. The most remarkable changes were found in animals subjected to repeated episodes of hypoglycemia. In these experiments there were recent and old changes in the distribution of the middle cerebral artery. The old changes were compatible with those induced by occlusion of the middle cerebral artery two to ten weeks before and have been described in detail elsewhere.[11] They consisted of hyperplasia of the endothelium of small vessels, glial nodules in a few zones of neuronal loss, and astroglial and fibroblastic proliferation at the site of occlusion of the middle cerebral artery. The recent changes are of special interest here and were sufficiently striking to permit the conclusion that they were due to localized hypoglycemia. In a wide territory supplied by the middle cerebral artery, including basal ganglia and cortex, there was recent necrosis or severe damage to nerve cells. In the hematoxylin and eosin preparations, such nerve cells were pale, eosinophilic, and homogenously stained (figure 10A). In the Nissl preparations, there was marked chromatolysis of these cells. Polymorphonuclear leukocytes and occasional lymphocytes were seen infiltrating these zones of neuronal necrosis. The white matter showed no abnormality. In some experiments, chromatolysis was present in the control hemisphere also, but not to the same degree as in the ischemic zone, and neuronal necrosis was not seen.

In two animals in which a hemodynamic crisis had been precipitated by a fall in blood pressure, recent endothelial damage with perivascular hemorrhage was present in the ischemic zone (figure 10B). In some vessels, polymorphonuclear leukocytes were present in vessel walls. These vascular changes were not present in animals in whom there had been no fall in blood pressure, and it was concluded that they were caused by ischemic anoxia secondary to the fall in blood pressure rather than due to hypoglycemia itself.

DISCUSSION

Reports that hypoglycemia may occasionally produce localized neurologic disorder in man have been confirmed by our own observations, and five illustrative cases have been presented. After recovery in case 1, hypoglycemia was proved to be the cause of the neurologic deficit, since careful reduction of the blood sugar reproduced both the symptoms and the electroencephalographic abnormality and administration of glucose promptly alleviated them. In case 2, in which localized neurologic signs appeared after prolonged hypoglycemia due to insulin-producing tumor of the pancreas, we were able to reproduce nystagmus by fasting, but the test was not carried to the point of further cerebellar signs.

In reviewing the literature, we have been unable to find a satisfactory explanation for the occurrence of localized neurologic disorder during hypoglycemia. We formed the hypothesis that, in the presence of a relative area of cerebral ischemia, hypoglycemia might produce a localized, reversible paralysis of neuronal function. It has been shown that other causes, such as a fall in blood pressure or anoxic anoxia, will produce a reversible paralysis of neuronal function in an area of cerebrovascular insufficiency. Experimental studies have demonstrated that, in the area of relative cerebral ischemia, any factor that temporarily decreases the metabolic supply or increases the cerebral metabolic rate may result in failure of local metabolic demand, with resulting temporary impairment of function.[10]

In the clinical cases reported here, it is presumed that a relative area of ischemia was produced by atherosclerosis in cases 1 and 5 and by a developmental anomaly of the circle of Willis in cases 2, 3, and 4. We have not had the opportunity to confirm this clinical impression at necropsy in any of our cases, nor did we feel that an attempt to prove this impression by vertebral and carotid arteriography was justified.

In the experimental animal, however, we were able to produce a localized neurologic deficit by inducing hypoglycemia after occluding the middle cerebral artery and to restore

neurologic function by the administration of glucose. Furthermore, these symptoms could be provoked repeatedly in the same animal. The neurologic deficit was readily produced by hypoglycemia alone, without concomitant fall in blood pressure. However, as might be expected from earlier studies,[10] if a fall in blood pressure occurred, a more permanent deficit resulted from complicating ischemic infarction. Provided that there was no fall in blood pressure, as was the case in all except two experiments, the neurologic deficit was demonstrated to be due to a progressive neuronal paralysis in which neuronal oxygen consumption in the ischemic territory was greatly decreased and was promptly restored to normal by the administration of glucose. During the stage of localized cerebral hypoglycemia, blood flow in the pial vessels appeared to be unchanged, but arteriovenous oxygen difference was reduced, as judged by the appearance of the venules which became orange-red. This change in arteriovenous oxygen difference was significantly greater in the ischemic area. The intravenous injection of Trypan blue during hypoglycemia showed no evidence of endothelial damage, provided a fall in blood pressure had not occurred.

Localized hypoglycemic paralysis appeared one-half to one hour after administration of regular insulin and was delayed for three to four hours if NPH insulin was used instead of regular insulin. The symptoms were provoked with ease in the fasting animal, but required larger doses if the animal had eaten. When the signs were maximal, the blood sugar was 10 mg. per 100 cc. of blood or less. Provided hypoglycemia was not prolonged, the depression of metabolic rate and functional impairment of cerebrum remained localized to the ischemic area. Continued hypoglycemia produced a more diffuse effect and the metabolic rate of the nonischemic hemisphere also became depressed. Administration of glucose produced some recognizable functional recovery beginning 20 seconds after the intravenous injection and recovery was usually complete within ten minutes. Prolonged and repeated episodes of hypoglycemia resulted in permanent functional impairment, and histologic examination of the brain showed acute necrosis and chromatolysis of nerve cells in the distribution of the occluded vessel.

Focal seizures of short duration were relatively common during the induction of hypoglycemia and also occasionally reappeared during the recovery stage after glucose had been given. During seizure activity, the cerebral metabolic rate of oxygen was temporarily increased (figure 7B), and after termination of the seizure, the functional deficit was severe. This experimental observation is of particular interest because focal seizures were followed by a posticta1 hemiparesis in one of our clinical cases (case 5).

Perfusion experiments in vivo[18] have shown that, if the blood supply is maintained well above normal, cerebral function continues in the absence of glucose for over an hour, but brain function ceases if blood flow is reduced. In these experiments, an increased elimination of nitrogen-containing substances was found in the perfusate derived from breakdown of proteins, lipids, and nucleic acid, indicating that in severe hypoglycemia the structural components of the brain itself are metabolized. In the experiments reported here, neuropathologic examination showed acute neuronal changes in the ischemic area after prolonged hypoglycemia compatible with metabolic utilization by the nerve cells of their own structural components.

These experimental observations indicate that, during hypoglycemia in the cat and monkey, glucose and probably glycogen stores are used up more rapidly in an area of relative ischemia than elsewhere in the brain, and as the supply of substrate fails, there is first a localized reduction of cerebral metabolic rate later followed by a more generalized effect. A similar generalized depression of cerebral metabolic rate has been observed in man during insulin coma therapy for schizophrenia.[19]

Our experimental data do not directly prove, but lend considerable plausibility to, the hypothesis that localized neurologic deficits accompanying hypoglycemia in man are due to a relative deficiency of blood supply, with resultant localized cerebral hypoglycemia.

SUMMARY

Clinical and experimental evidence has been presented to show that in the presence of a relative area of ischemia of the brain, hypo-

glycemia produces a localized reversible paralysis of neuronal function, with resultant motor and sensory deficit. During this stage of paralysis, metabolic utilization of oxygen may be demonstrated to be impaired. Administration of glucose restores normal functional activity and oxygen consumption to the area of hypoglycemic brain. It is presumed that the localized neuronal paralysis is the result of a reduced availability of glucose in the ischemic area and that the administration of glucose rapidly restores the deficient substrate. If sufficiently prolonged, localized hypoglycemia becomes irreversible and necrosis of nerve cells occurs.

Dr. Geraldine Hardy assisted in the investigation of case 1.

Dr. J. L. Chason, professor of neuropathology, Wayne State University, made the neuropathologic studies.

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■ The causes of apoplexy may be considered as they predispose or render persons liable to the disease, and as they excite or actually produce it.

Among the *predisposing causes* of apoplexy, some authors mention hereditary conformation.—Forestus relates the cases of four persons of the same family, a father and his three sons, who died of this disease, which he observes was truly hereditary; and Portal, in his account of *l'Apoplexie Plethorique* states, that he has seen many families in which this species was "come hereditaire." Wepfer and many others are of the same opinion.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Epileptic cephalea

L. Halpern, M.D. and E. Bental, M.D.

UNTIL RECENTLY the relationship between headaches and epilepsy has been investigated mainly in connection with the problem of migraine and epilepsy. The following observations would appear to demonstrate the existence of headaches which are the sole clinical manifestation of an epileptic activity.

CLINICAL AND ELECTROENCEPHALOGRAPHIC FEATURES

Case 1. An 11 year old girl came to the outpatient department for the first time in 1953 complaining of severe, continuous headaches — with paroxysmal aggravation — localized in the forehead and temple region. The general physical and neurologic examinations, including a roentgenogram of the skull, did not show any abnormal findings. No emotional background which might account for her complaint could be found. The headaches appeared to be of organic origin. The electroencephalogram showed a resting record with alpha rhythm of 10 cycles per second, sometimes irregular, with runs of slow waves accompanied occasionally by sharp waves and spike-and-wave-like complexes (figure 1). On overbreathing, this abnormal activity became more noticeable (figure 2). During photic stimulation with seven to 15 flickers per second, there appeared generalized bursts of spikes and slow waves, sometimes in typical spike-and-wave pattern of three cycles per second, especially on eye closure (figure 3).

The electroencephalographic findings led us to inquire further into the personal and family history. It was thus learned that the girl's younger sister had febrile convulsions for a short period in her early childhood. The patient was delivered with the aid of forceps, and during her first week of life she had had a number of convulsive seizures. Since then, however, she had been free of any epileptic manifestations.

In view of the typical epileptic electroencephalogram and anamnesis, systematic anticonvulsive treatment was instituted, whereupon the headaches abated. The girl, after feeling well for a few months, decided of her own accord to stop all treatment. Three years later she was back at the outpatient department complaining of renewed headaches. On repeating the electroencephalogram, the same record was observed, with especially noticeable generalized bursts of spike-and-wave-like complexes during photic stimulation. As soon as the patient received anticonvulsant treatment, the headaches disappeared. Once again, no neurologic abnormalities were found. The girl still suffers periodically from headaches, but, in her own words, these are not to be compared with the pain she had before commencing treatment. A recent electroencephalogram showed the same typical record.

It may be assumed that there was an epileptic trend in the patient's family which revealed itself in the girl by convulsions during her first week of life. Thus, the history of the patient, the characteristic electroencephalogram, and the striking effect of anticonvulsant treatment seem to justify the assumption that the headaches in her later life were the sole manifestation of an epileptic activity.

Case 2. An 11 year old boy came to the outpatient department for the first time in 1955 complaining that for the past year he suffered from headaches, dizziness, nausea, and vomiting. The mother had been told that the boy suffered from "migraine." Whenever the boy had such an attack, he experienced dizziness and nausea. He would lie down for a while, fall asleep, and awaken without any complaints. The general physical and neurologic examinations revealed no abnormal findings. The electroencephalogram showed a resting record with a regular background activity containing high alpha waves of 10 cycles per second, which blocked on eye opening. Single waves of theta frequency appeared occasionally. During overbreathing, there was a slight slowing down of frequency and increase of amplitude, the alpha waves became peaked and were mingled with slow waves of theta frequency, sharp waves appearing occasionally. On photic stimulation with nine flickers per second, particularly on eye closure, general bursts of five cycles per second waves and spikes were recorded. On increasing the flicker frequency, clear bursts of spike and wave activity, slow waves, and multiple spikes appeared (figure 4). The examining physician noted on the patient's chart that, had it not been for the clear electroencephalographic record, he would never have considered epilepsy in this case. Since then the boy has undergone a number of control electroencephalograms which all showed the same record. The boy was given anticonvulsant treatment, and the number of attacks of headache diminished markedly. When on one occasion he stopped treatment for a short period, numerous and severe

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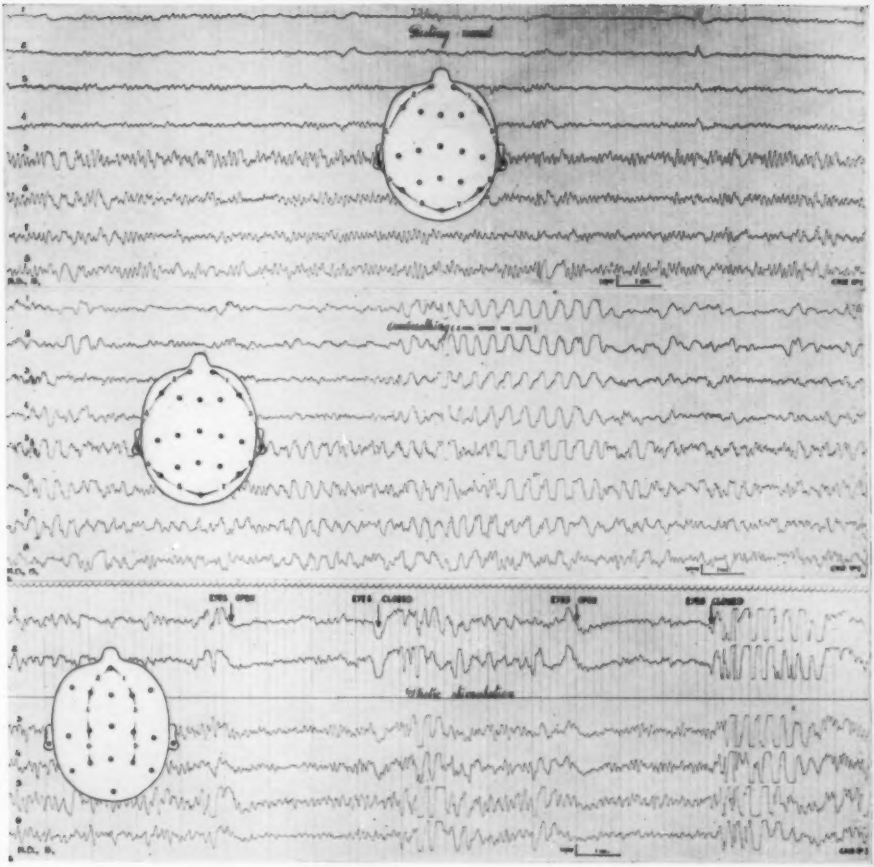

FIG. 1. (top) *Case 1.* resting record.
FIG. 2. (center) *Case 1.* Overbreathing, two minutes after the start.
FIG. 3. (bottom) *Case 1.* Photic stimulation.

headaches recurred immediately; they subsided only after reinstitution of treatment. During the autumn of 1956, while the headaches had subsided, the boy wet his bed three times. A routine electroencephalogram done in August 1957 revealed the same typical features during photic stimulation.

In this case our first impression was that the episodes of headache and dizziness were of migrainous origin, particularly in view of a "migraine" trend in the family. But the clinical signs did not follow the characteristic pattern of migraine. Moreover, the electroencephalogram and the results of anticonvulsant treatment seemed to justify the assumption that, although there was no history of epilepsy in the boy's family and although the boy himself never suffered from any kind of typical epileptic seizures, these spells of headaches were a manifestation of epileptic activity.

Case 3. A seven year old girl came to the outpatient department for the first time in 1953. According to the mother, the child had complained of severe pains in the forehead. These episodes were often accompanied by pallor, nausea, and sometimes vomiting. They appeared approximately once a week and lasted for several

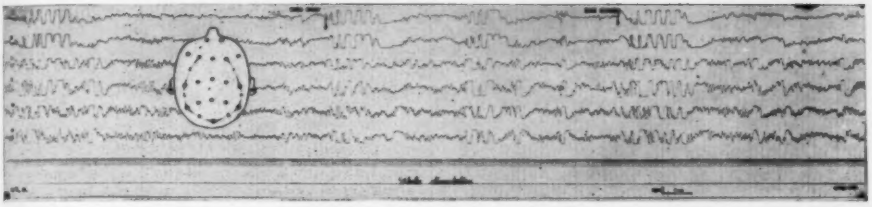

FIG. 4. *Case 2.* Photic stimulation.

hours. From the family history it was learned that her mother suffered from "migraine." The girl's past history was negative. No abnormal findings were elicited on physical and neurologic examinations. A roentgenogram of the skull and sinuses was normal. Analgesic treatment, as well as trial treatment with cafergot, was of little avail. The examining doctor recorded at that time that it was not a typical picture of migraine. In 1955 the girl visited the pediatric outpatient department complaining of almost daily attacks of headaches, now unaccompanied by nausea or vomiting. Physical and neurologic examinations were again negative. The possibility that these headaches might be an epileptic equivalent was considered. The electroencephalogram revealed an irregular background activity and alpha waves of nine to 10 cycles per second, with variations in amplitude and frequency. On overbreathing, there appeared discharge of high amplitude waves three cycles per second, occasionally accompanied by small spikes (figure 5). During photic stimulation with 14 to 19 flickers per second, bursts of multiple spikes were recorded on eye closure (figure 6).

In view of these findings, anticonvulsant treatment was given. The paroxysmal attacks disappeared, leaving some vague continuous pain. Since then the girl has been under constant medical supervision and has been feeling much better. As soon as she tried stopping treatment, the severe headaches recurred. Control electroencephalograms showed the same characteristic patterns both during overbreathing and photic stimulation.

Here again, the first impression was that these headaches were not of migrainous origin. The electroencephalogram and the results of anticonvulsant treatment led us to assume that the headaches were the only manifestation of an epileptic activity.

Case 4. A 14 year old girl began to complain of severe pains in the forehead which persisted for hours. Her past history was not significant. The general physical and neurologic examinations revealed no abnormalities. No family history of migraine or epilepsy could be elicited. The electro-

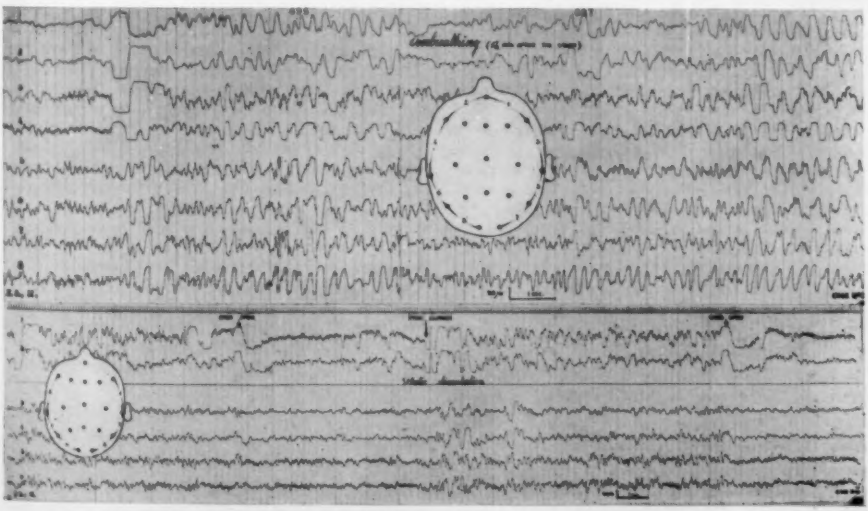

FIG. 5. (top) *Case 3.* Overbreathing, one and one-half minutes after the start.
FIG. 6. (bottom) *Case 3.* Photic stimulation.

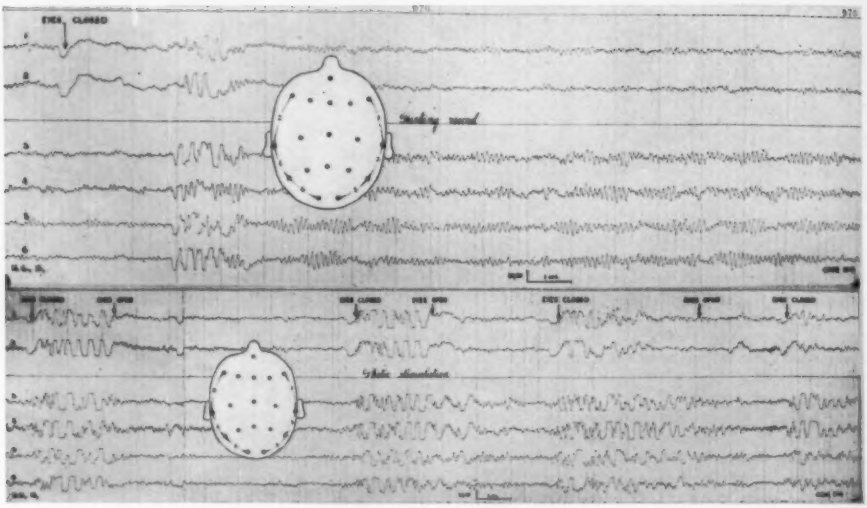

FIG. 7. (top) *Case 4.* Resting record.
FIG. 8. (bottom) *Case 4.* Photic stimulation.

encephalogram showed regular background activity, with alpha of nine cycles per second, which blocked on eye opening. In the resting record, after eye closure, one single burst of three to four cycles per second mingled with spikes appeared (figure 7). During photic stimulation with eight flickers per second, on eye closure generalized bursts of spike and wave activity and slow waves and spikes lasting for two to three seconds appeared (figure 8). In view of this record, the possibility that this was a case of epileptic cephalea was considered. Treatment was instituted and the patient reported general improvement. In September 1955 the patient returned complaining of persistent and severe occipital headaches, sometimes increasing in intensity in the early hours of the morning. She seldom felt nausea. An electroencephalogram revealed the same typical epileptic activity, now appearing only during photic stimulation. Questioning revealed that she had discontinued anticonvulsant treatment. With treatment restored, her condition improved. During 1956 she was examined several times, and was almost entirely free of headaches.

This girl, who was seen for the first time at the age of 14 and had been under clinical observation for three years, had never suffered from any usual known manifestation of epilepsy, nor was there a history of seizures in her family. As in the previous patients, anticonvulsant therapy was most effective.

Case 5. A ten year old girl was seen in the pediatric outpatient department in January 1957. She complained of continuous headaches, with paroxysmal aggravation, over a period of 18 months. In addition, she had often had episodes of subfebrile temperature, which ceased after tonsillectomy. However, the headaches persisted, localized in the right forehead region or as generalized diffuse pains in the whole head. The physical examination revealed a systolic murmur grade II at the apex. Otherwise, there were no abnormal findings. Except for a slight blurring of the right optic disk without pathologic significance, no neurologic abnormalities were noted. The visual field was complete. Roentgenograms of the skull and chest were normal. Ear, nose, and throat examination was normal. The resting electroencephalogram showed a slightly irregular background activity, with alpha activity of 10 cycles per second. During photic stimulation with 19 to 20 flickers per second, on eye closure there occurred bursts of slow waves and spikes (figure 9). Control electroencephalograms done subsequently over a period of six months showed normal resting records. During photic stimulation at 20 flickers per second and onward, there occurred again bursts of slow delta waves and spikes, mainly on eye closure. Anticonvulsant treatment produced only a transitory improvement.

On the basis of the electroencephalographic findings, there is good reason to assume that the cephalea in this case is of epileptic origin, although anticonvulsant treatment with Hydantoin and Luminal has not as yet given the expected results.

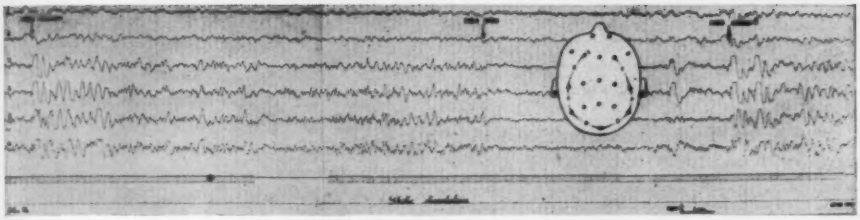

FIG. 9. *Case 5.* Photic stimulation.

COMMENT

The occurrence of headaches in connection with epileptic seizures, either before the attack, following a seizure, or during the interseizure period, has been a well established fact since the classical publications of Gowers and Jackson. The most striking feature in the cases described above, however, is that the patients never suffered frank epileptic seizures, except for one who had convulsions during the first week of life only. The headaches appeared either paroxysmally or as continuous headaches during long stretches of time, with periodic aggravation. The real nature of these headaches was elucidated by the electroencephalographic tracing, especially during photic stimulation. A slightly dysrhythmic and slow activity was already noted in the resting record of all five patients. Overbreathing accentuated this abnormal activity. The epileptic nature of these headaches was finally established by photic stimulation, which showed as a common feature in all these cases paroxysmal outbursts of multiple spikes or spike-and-wave activity appearing mainly on eye closure. The good clinical effect of anticonvulsant treatment, which either stopped the headaches or diminished them markedly, should also be taken into consideration.

All these observations led us to consider the headaches as a manifestation of an epileptic disorder. Epileptic cephalea presents a clinical manifestation parallel to other forms of "masked epilepsy," such as abdominal epilepsy in which the paroxysmal abdominal pains may be the sole symptom of this disease. Similar observations of headaches as the only expression of epileptic disorder were made by Waggoner and Bagchi,[1] who reported 15 cases of paroxysmal, moderate to severe headaches occurring in individuals whose electroencephalogram revealed borderline and abnormal potentials and frequencies. In these cases which they called "epileptic variants," there is no mention whether photic stimulation was used. Livingston[2] also stated that recurrent headaches may be the only clinical manifestation of an epileptic disorder. He described 14 children who had suffered recurrent paroxysmal headaches, although none of the patients had ever had frank convulsions. In eight of these cases, electroencephalographic studies revealed abnormalities which consisted predominantly of abnormally slow activity. Photic stimulation was not mentioned as having been applied in these cases, but anticonvulsant therapy showed good results in nine of the 14 cases. Wallis,[3] while reviewing the various forms of "masked epilepsy," also mentioned a group of three children suffering from headaches. These children had attacks of headaches for different periods of time but never had typical epileptic seizures. The electroencephalograms of all these children were abnormal and indicative of epilepsy. No detailed electroencephalographic report is given, unfortunately, so that it is not known whether any of these children were subjected to photic stimulation. Only Heyck and Hess[4,5] stressed for the first time the importance of epileptic seizure discharges on photic stimulation in patients suffering from so-called vasomotor cephalea.

In view of our experience based on a greater number of cases than described above, and taking into account the experiences of Heyck and his co-worker, epileptic cephalea would appear to be a well defined clinical entity. It should be emphasized that epileptic cephalea must be clearly differentiated from migrainous headaches. None of the reported patients with epileptic cephalea presented the typical clinical symptoms of migraine. Heyck,

reviewing a series of migraine cases, found electroencephalographic abnormalities in the form of hypersynchronic rhythms, but never the typical epileptic discharge seen during photic stimulation.

Our experience also corresponds to that of Heyck with regard to the influence of anticonvulsant treatment. Although anticonvulsant treatment brought about clinical improvement, the electroencephalographic record remained pathologic in the follow-up over a period of years.

Considering these observations, it seems justified to single out epileptic cephalea as a special form of headache.

SUMMARY

Five cases of paroxysmal headaches in children are described.

The nature of the headaches was clarified by electroencephalograms, which revealed epileptic activity in all cases, especially during photic stimulation.

With the exception of one who had convulsions in the first week of her life, none of these children had experienced frank seizures.

Epileptic cephalea seems to appear as the sole manifestation of a latent epileptic tendency and deserves a special place among the various forms of headaches.

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■ The terminations of epilepsy are likewise various. After frequent attacks, it sometimes ends in apoplexy, sometimes in paralytic affections, particularly of the nerves necessary to hearing and vision; but its common termination is in idiotism or fatuity. The faculties of the mind, especially the judgement, the memory, and the imagination, gradually fail, and a total imbecility supervenes. Innumerable instances of this kind might be quoted from Van Swieten, Tissot, and others. I know no author who has more impressively described the wretched state of those who have long laboured under this disease, than Aretaeus, in the fourth chapter of his first book, De Causis et Signis Acutorum Morborum.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Therapy of acute, chronic and mixed hepatic porphyria patients with chelating agents

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THE EFFECTIVENESS of the chelating agents 2,3-dimercaptopropanol (BAL) and ethylenediamine tetraacetic acid (EDTA) in the therapy of acute, chronic, and mixed porphyria patients with severe neuropsychiatric symptoms has been reported in 15 of 20 patients treated with these agents.[1-3] Individual cases have been cited[4,5] in which BAL therapy seemed effective in arresting advancing symptoms of acute porphyria. Schrumpf[6] reported that a case of chronic porphyria with cutaneous symptoms benefited under BAL therapy. Paul and Thyresson[7] reported that a case of chronic porphyria improved with BAL therapy, while Dean[8] treated an acute porphyric patient with BAL for one day and felt it was ineffective. Kehoe, Rudensky, and Reynolds[9] likewise treated one of two acute porphyric twins with low dosage of BAL for ten days but felt it was ineffective, although subsequently the patient went on to recovery from neurologic and psychiatric symptoms without other medical therapy during hospitalization. A mixed porphyric with porphobilinogenuria (included in a previous series) was reported in detail by Woods, Peters, and Johnson[10] to illustrate the favorable influence of EDTA administered initially by the intravenous route, followed by maintenance on oral EDTA therapy, resulting in continued recovery and protection from cutaneous symptoms.

This report is to re-emphasize the effectiveness of chelation therapy in hepatic porphyria. Evidence will be presented to indicate the apparent existence of a porphyric-schizophrenic syndrome; another group of patients, who were clinically acute porphyrics but excreted porphobilinogen rarely, will be designated the "paraporphyric" group. It would appear that the chronic and mixed porphyric consistently excreted urinary copper in excess, while the acute porphyric often showed zinc diuresis before and during chelation treatment. Finally, an alteration of tryptophan metabolism was seen in the acute, chronic, and mixed hepatic porphyric, the porphyric-schizophrenic, and the "paraporphyric" patient.

Watson[11] divides porphyria into two major forms: first, the porphyria erythropoietica, in which the metabolic error resides in the bone marrow with onset in infancy of mutilating photosensitive dermatitis, and second, the hepatic porphyrias which he subdivides into acute, cutanea tarda, mixed, and latent forms. Acute hepatic porphyria, inherited as a mendelian dominant, is characterized by recurrent gastrointestinal, psychiatric, and neurologic symptomatology occurring singly or in combination. Whereas erythropoietic porphyria is rare, we are of the opinion that hepatic porphyria is much more common than suspected. Hepatic cutania tarda porphyria is manifested by the late onset of photosensitive cutaneous lesions. Hepatic mixed porphyria incorporates a combination of the cutaneous and acute varieties in which cutaneous, neurologic, psychiatric, and abdominal symptomatology appear in varying combinations. Latent forms of the disease exist. Increased delta-amino levulinic acid in the urine in acute porphyrics, as reported by Granick and Vanden Schrieck[12] and by Mauzerall and Granick,[13] stimulated us to utilize the quantitative determination of delta-amino levulinic acid, a porphobilinogen precursor, as a useful screening device. Eleva-

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tion of fecal protoporphyrin determined by Dean's method[14] was communicated to us by Eales.[15] With few exceptions, we noted elevation of fecal protoporphyrin in the verified porphyrics and used this test also in screening for likely porphyric patients. Elevation of urinary zinc from two to 36 times normal before chelation, as previously reported,[2,3,10] seemed to parallel symptoms more closely in the acute porphyric during exacerbation than did abnormal porphyrin excretion. A more recent observation concerns elevation of urinary copper up to three to six times normal in our chronic and mixed porphyric patients.

Quantitative determination (method of Mauzerall and Granick[13]) of porphobilinogen and delta-amino levulinic acid and qualitative determination of coproporphyrin, uroporphyrin, copper, and zinc urinary excretion were then applied to cases showing elevation of fecal protoporphyrin in whom clinical symptoms suggested the diagnosis of porphyria. Since porphyria patients will demonstrate porphobilinogen and uroporphyrin excretion often intermittently, as suggested in the term "acute intermittent porphyria," multiple Watson-Schwartz tests for porphobilinogen may be necessary to rule out the metabolic disorder when the clinical inventory is highly suggestive (cases 2 and 4). Dean and Barnes[14] suggest that the term "hyperporphyrinism" be applied to those patients showing an increase of porphyrin production and excretion without a genetic basis. In the present study, the term paraporphyria has been applied to those patients clinically resembling the known porphyric group, but in whom porphobilinogenuria may be scanty. Many of these patients manifested increased fecal protoporphyrin, elevation of delta-amino levulinic acid, and, at times, increased urinary zinc or copper. Further studies in some of our paraporphyric group have revealed a positive Watson-Schwartz test on occasion.

CASE MATERIAL

Our material includes 47 patients who have been studied in this manner. Following Watson's classification, this group includes 32 acute hepatic porphyrics, one chronic hepatic porphyric, five mixed hepatic porphyrics, and 12 paraporphyrics. There were 34 women and 13 men, ranging in age from 15 to 65 years. Thirty-seven patients were treated with chelating agents, either BAL or disodium calcium EDTA, and included 24 acute intermittent hepatic porphyrics, eight paraporphyrics, and five mixed hepatic porphyrics.

CLINICAL SYMPTOMS

Ten patients showed bulbar symptoms in the form of dysphagia, diplopia, anisocoria, dysarthria, facial paresis, and laryngeal palsies. Tracheotomy had to be performed in four patients. Grand mal seizures occurred in ten patients. Jacksonian seizure activity in two patients was accompanied by focal electroencephalographic localization, with hemianopsia, alternating from one side to the other; status epilepticus of 10 to 15 seizures per day was seen in one patient (case 2). "Fainting" attacks or recurring episodes of muscular asthenia were observed. Cerebellar ataxia as well as extrapyramidal symptoms have been seen to occur in several patients, one of whose paraporphyric symptoms were precipitated by Dilantin intoxication and progressed over a two-week period despite Dilantin withdrawal. BAL treatment resulted in dramatic recovery.

PSYCHIATRIC SYMPTOMS

Psychiatric symptoms were present in over 58 per cent of the patients. Toxic psychosis in 15 patients was characterized by bizarre catatonic excitement, misidentifications, deja vu, and auditory and visual hallucinosis. At other times the level of consciousness ranged from torpor to coma. Four of the toxic psychotic group had a picture suggesting schizophrenia, including a flattened affect and paranoid ideation prior to their more acute illness. Another 13 patients, including five paraporphyrics, were clinically identical to the schizophrenic, as confirmed by the Rorschach test in several cases, as well as by independent psychiatric evaluation. Nine of our acute porphyrics demonstrated only abdominal symtomatology. Of this number, six appeared clinically addicted to Demerol or other drugs. Addiction and polysurgery may point to porphyria as the true cause.

PERIPHERAL NERVOUS SYSTEM SYMPTOMS

Ten patients presented peripheral neuropathy, with complete tetraparesis in six, para-

plegia in two, and monoplegia in one. One patient revealed a dysesthetic trigeminal neuralgia. Case 3 showed a venous vasculitis on muscle biopsy and another showed periarteritis nodosa, whereas muscle biopsy in several other cases revealed normal muscle. Of ten patients with severe peripheral neuropathy, we have obtained complete recovery on treatment with chelating agents in five, with continuing improvement in two currently under therapy. One of these patients (previously reported[2]) responded to ACTH, after chelation with BAL apparently failed. Paresis caused by porphyria is as often distal in onset as proximal and may be accompanied by recurrent myoclonic jerks, asynchronous muscular contraction (especially against resistance), delayed volitional response, and generalized involuntary motor excitation upon volitional motion of a single extremity. This heightened motor irritability may exist, despite complete tetraplegia. Muscle and joint pains may be severe during the onset of a paralysis and again in the recovery phase, although objective sensory changes are seldom present. Pain may be vague and poorly localized, perhaps reflecting an altered level of consciousness. One patient had a fracture dislocation of the right shoulder without pain until after her lowered level of consciousness was improved following BAL treatment.[2] Differentiation from conversion syndromes may be difficult. Abdominal, back, or chest pains are frequent; those with severe back pain often assumed a knee-chest position. Multiple laparotomies were performed under Pentothal anesthesia in two patients and a pneumoencephalogram was done in one. Laminectomy had been performed in two patients who were thought erroneously to have had a cord tumor.[2]

GASTROINTESTINAL SYMPTOMS

Obstipation was noted at various times in half of the patients; diarrhea was seen in three cases, one of whom had frequent bloody stools.[3] Fecal impactions occurred frequently during acute exacerbations.

GENITOURINARY SYMPTOMS

Temporary oliguria, dysuria, incontinence, and urinary retention were associated with suprapubic pain. The "Burgundy wine" or brownish urine described as typical in textbooks was seldom mentioned. Even in the most severe cases, the urine was occasionally of normal color that did not change to brown, red, or black after exposure to sunlight and acidification, despite the presence of porphobilinogen in the urine. The urinary odor was often offensive, as noted by the nurses and the patients themselves.

DERMATOLOGIC SYMPTOMS

A malar flush over the "butterfly area" was a frequent finding during the acute onset of neuropsychiatric symptoms. Other patients had a diffuse, dusky complexion; hirsutism was noted often. Cutaneous bullae were seen in three mixed hepatic porphyrics and in one chronic porphyric, whereas a dusky, often "metallic" complexion and melanosis (especially over light-exposed areas) was seen in 15 patients, including three paraporphyrics and three mixed porphyrics. Photosensitivity was noted in three patients, and intolerance to oil-based paints and chemical solvents occurred in ten patients. Barbiturates and occasionally ingestion of peas, corn, and tomatoes seemed related to exacerbations of the disorder. Periorbital and parotid swelling related to exacerbations of illness and accompanied by zinc diuresis and gastrointestinal symptoms was seen in one patient.

METHODS OF TREATMENT AND AGENTS USED

BAL was used in a 10 per cent solution in 20 per cent benzyl benzoate in peanut oil. Doses ranged from 50 to 1,200 mg. per 24 hours in divided doses. Therapy varied from four to 60 days consecutively. In several cases one to three injections of 100 to 300 mg. weekly for as long as two years have been employed. With the exception of a questionably related transient erythema multiforme, no toxic effects of BAL or EDTA have been encountered. Two patients developed sterile abscesses at the injection site. In 26 cases BAL was the only agent used. In seven patients BAL was combined with intravenous EDTA in either acute or chronic phases of the disorder. EDTA alone was used in four. EDTA intravenous dosage varied from 1 to 10 gm. in a 24-hour period, diluted in 5 per cent glucose in water

in a ratio of 2.5 to 5 gm. of EDTA per 1,000 cc. The medication was administered over two to four hours, and two to five consecutive days constituted the usual course of treatment. Fourteen days of total treatment were reached in one case. Oral EDTA in 0.5 gm. tablets was occasionally used in subacute phases, the daily dose varying from one to three tablets. Two patients received hydrocortisone for several days during chelation therapy because of oliguria, and diuresis followed promptly. The choice of chelating agent depended in part on a history of lead exposure, but EDTA was used preferentially. Urinary lead excretion levels were borderline in several cases and lead diuresis was noted during chelation.

After the diagnosis has been made or suspected, barbiturates, sulfonamides, alcohol, heavy metals, exposure to oil-based paints, solvents, and sunbathing must be studiously avoided. Thorazine, Demerol, paraldehyde, Frenquel, and intravenous procaine were used very occasionally, and they were needed infrequently during chelation or thereafter.

In addition to our chelation regimen, exceptional nursing care, tracheotomy, and careful attention to fluid and electrolyte balance must be credited in bringing about clinical recovery.

In our laboratory the following are accepted as upper normal values in the urine: porphobilinogen, 1.0 mg./l.; delta-amino levulinic acid, 2.5 mg./l.; zinc, 0.5 mg./l.; lead, 0.05 mg./l.; copper, .03 mg./l.

RESULTS OF CHELATION TREATMENT

A total of 37 patients have been treated, including 24 acute hepatic porphyrics, five mixed hepatic, and eight paraporphyric patients. Thirty-one responded favorably to chelation therapy, three showed equivocal reactions, and three were classed as failures. One patient died with periarteritis nodosa which was diagnosed by biopsy prior to chelating efforts. This patient had not responded to previous continued therapy with ACTH and cortisone.

All of the paraporphyric group, as well as the mixed porphyrics, benefited from chelation schedules. Thirteen of the acute porphyrics and two of the mixed porphyrics were in very critical condition from advanced neuropsychiatric symptoms prior to chelation therapy, despite prior ineffectual use of ACTH in four cases. All but two of this group seem to have benefited by treatment, with complete recovery from a tetraparesis in four. Two additional patients with tetraplegia were treated with chelating agents and are currently recovering from their paralysis. However, one tetraparetic derived benefit from ACTH after BAL treatment seemed inadequate.[2] One patient with dorsal transverse myelitis and peripheral motor neuropathy of the upper extremities recovered function of her arms and hands after chelation therapy, but the myelopathy was unchanged. Since recovery from paralysis due to peripheral neuropathy may require regrowth of peripheral axons, it is important that physical therapy be continued throughout convalescence that may take many months.

Psychiatric symptoms including schizophrenic symptoms improved with chelation therapy.

Abdominal symptoms were ameliorated and cutaneous symptoms normalized. Our chronic porphyric patient was not chelated because of co-existing nephritis.

OTHER TREATMENT

Response of the psychotic symptoms to Frenquel previously reported[2,3] has been seen in two additional cases, suggesting that the porphyric psychiatric complex is analogous in part to a lysergic acid psychosis which, as we know, is aborted by Frenquel administration.

Once the diagnosis was established or suspected, barbiturates, alcohol, heavy metals, sulfa drugs, exposure to oil-based paints and solvents, and sunbathing were avoided. Chlorpromazine was used occasionally for symptomatic relief of abdominal colics, though, in general, continued chelation with oral EDTA or BAL injections lessened the need for other agents.

HEAVY METAL AND TRYPTOPHAN STUDIES

Studies of tryptophan metabolism in the hepatic porphyrics by Price, Brown, and Peters[16] revealed a marked elevation of urinary kynurenic acid or kynurenine, or both, after a loading dose of tryptophan, during acute stages of acute, chronic, and mixed porphyria resembling the tryptophan metabolic pattern seen in patients with scleroderma by Ruka-

vina, Mendelson, Price, Brown, and Johnson.[17,18]

Patients in the paraporphyric group shared this anomaly of tryptophan metabolism. Clinical recovery was often associated with restoration of normal tryptophan metabolism.

Before chelation, elevation of urinary zinc was noted in 12 of 18 acute porphyric patients who responded to chelation therapy. Copper excretion was elevated in six of the chronic and mixed porphyrics studied, five of whom were chelated. Increased urinary excretion of both copper and zinc was noted before chelation in seven acute patients. The values for elevated copper excretion before chelation ranged from two to five times the norm, for zinc from two to 36 times the norm. A positive correlation exists in some patients between the activity of porphyric symptoms and the levels of zinc urinary excretion. The zinc diuresis occurring during chelation in the acute porphyric approached normal figures during the recovery phase, despite continuance of chelation and continued elevation of abnormal porphyrin excretion in some patients.[3] A copper diuresis during chelation is noted in the chronic and some of the mixed group of porphyrics. Improvement in clinical symptoms was observed early during a course of chelation therapy, suggesting that addition of EDTA and BAL tends to normalize the metabolic disturbance.

DISCUSSION

As previously suggested by Peters and coworkers,[1–3,10] excretion of coproporphyrin, uroporphyrin, porphobilinogen, and delta-amino levulinic acid may be indicative of a metabolic block due to an excess of cation zinc or perhaps other cations. The body's natural chelating mechanisms might decompensate with unusual stress or load of blocking cations. The appearance of abnormal porphyrin metabolites may constitute nature's attempt to mobilize these porphyrin substances for the needed purposes of chelation. It is known that coproporphyrin and uroporphyrin are excreted in acute porphyria in both urine and feces as a zinc metal complex, according to Watson and Schwartz.[19]

Günther[20] recognized that urinary porphyrins in porphyria patients are often partly combined with a metal. Watson and Larson[21] called attention to the zinc complex being relatively larger in a case of porphyria showing relapse. Derrien and co-workers[22,23] described zinc uroporphyrinuria and ascribed a protective or detoxifying action to the zinc cations. If the role of zinc is protective or detoxifying in nature, it would be difficult to explain the effectiveness of chelation, which increases zinc and copper diuresis in the porphyric. We suggest that diversion of these metabolic building stones for purposes of chelation constitutes an innate defensive effort to remove blocking cations from the body. Appearance of abnormal porphryins in the urine, therefore, is an extremely serious sign, as is borne out by the reported high mortality rate in the acute porphyric cases showing neuropsychiatric symptoms (up to 90 per cent[1–3]). Perhaps a reinforcement of the natural chelating pool by EDTA and BAL removes an enzymatic block due to these cations (zinc, copper, or others), allowing a normal mechanism to be re-established. That chelation effect is present in other drugs and natural metabolic processes is summarized admirably by Chenoweth[24] and by Bessman and Doorenbos.[25]

We have reviewed the important or essential role of zinc ions in the metallo-enzymes, such as carbonicanhydrase, uricase, catalase, peroxidase, carboxypeptidase, lacticdehydrogenase, and alcoholdehydrogenase.[3] An excess of zinc is said to inhibit the enzymatic activity of lacticdehydrogenase.[26] Gonadotropin[27] and insulin activity is retarded by 40 per cent on addition of zinc.[28] Activity of ACTH likewise can be slowed by addition of zinc. Symptoms in acute porphyria might be due more to the effect of cation blocks on these metallo-enzyme systems than by diversion of porphyrin metabolites from the body.

Kluver,[29,30] however, in a discussion of the free porphyrins of the central nervous system, showed that certain regions of the central nervous system show red fluorescence on exposure to near ultraviolet light. The fluorescence maxima and solubility properties indicate that the porphyrin present in greatest amount is coproporphyrin, with a smaller amount of protoporphyrin. Kluver's findings were confirmed by Blanshard,[31] who succeeded in isolating coproporphyrin, predominately type III isomer. Klu-

ver suggested a relationship between this fluorescence noted in warm blooded animals and not noted in reptiles, amphibians, and fish, and postulated a relationship between porphyrins and temperature regulation. He described an "ascending porphyrinization" reminiscent of the "ascending myelinization" in the central nervous system. This ascending porphyrinization first appears over the ventral aspects of the cord, then in the fiber masses of the brainstem, cerebellum, and cerebrum, and finally, in the commissures of the cerebral hemispheres. In the rat fluorescence is absent at birth but appears in the spinal cord at the age of 25 days. This same period is also particularly significant in the development of myelinization, vascularization, and motor activity in the rat. Porphyrins occur predominantly in oligodendroglia. Kluver noted an inverse relationship between the amount of free porphyrin and the amount of cytochrome that existed in various areas of the central nervous system and suggested that coproporphyrin was derived from cytochrome. Individuals presenting a continually disturbed porphyrin metabolism excrete abnormal porphyrin under minimal as well as maximal stress.

It is our feeling, however, that, as certain portions of the body's chelation ability are exhausted by stress, the porphyrin-cytochrome system may be ultimately involved in an adaptive mechanism giving rise to abnormal excretion of porphobilinogen, delta-amino levulinic acid, fecal protoporphyrin, as well as uroporphyrin and coproporphyrin (chelated with zinc, copper, or other heavy metals), with copper primarily present in the chronic and mixed porphyric.

An acquired porphyria would seem possible and could explain patients with alcoholism, cirrhosis, and lead intoxication who excrete coproporphyrin and, on occasion, traces of porphobilinogen.

Our observation of increased urinary copper excretion before chelation in the mixed and chronic porphyric, as opposed to the acute porphyric with elevation of urinary zinc, suggests that two different metabolic blocks can occur.

The importance of copper cations to human nutrition is summarized by Gubler,[32] who called attention to its role in uricase, tyrosinase, and cytochrome oxidase in mammalian tissues, suggesting copper's fundamental role in the oxidation-reduction reactions and energy transfer in cells. Copper catalyzes the closure of the sulfhydryl groups and the keratin molecule to form disulfide bridges. In ruminants, copper has been found to play a role in the maintenance of normal myelin sheath.

In the chronic and mixed porphyrics, alteration in tyrosine metabolism (dependent on copper) leads to light-, heat-, or physically-induced skin changes; in the acute porphyric the splanchnic or central nervous system is primarily involved, perhaps due to involvement of other metallo-enzyme systems. The frequent appearance of porphobilinogen and delta-amino levulinic acid in the acute porphyric group, and rarely in the mixed and chronic porphyric, suggests that the block may be before the delta-amino levulinic acid stage in the chronic porphyric due to copper excess, while that of the acute porphyria might be due to a block further along the metabolic pathway. The enzyme for conversion of delta-amino levulinic acid to porphobilinogen has been identified by Gibson, Neuberger, and Scott.[33] Since acute porphyrics occasionally develop skin changes (tanning, increased pigmentation, hirsutism, and occasionally bullous formation) and the chronic porphyric may, as in four of our cases, show central nervous system involvement, it seems that the two systems may merge.

The most innocuous and historically earliest symptoms in many of the acute porphyric patients consist of abdominal colic or back pain. At this stage Pentothal or other barbiturates, sulfa drugs, undue exposure to oil-based paints, alcohol, or sunlight may precipitate a more serious involvement of the central nervous system. Alterations in blood-brain barrier might explain a spread of porphyric symptoms from the peripheral and autonomic nervous system to the central nervous system. Since withdrawal of porphyrins may impair myelin metabolism, as noted by Kluver, this could explain certain fleeting or vague symptoms noted. The focal electroencephalographic findings during exacerbations in three patients, as well as a transverse myelitis in two, suggest that a disturbed metabolism may affect local tissue levels. When hypothalamic areas are involved, schizophrenic and other psychiatric symptoms become manifest.

That marked neuropsychiatric symptoms can occur in the absence of concomitant abnormal porphyrin excretion is illustrated by case 2, in whom positive Watson-Schwartz tests and traces of uroporphyrin excretion were present only occasionally during her first University Hospital admission. This may suggest that a metabolic block occurred in a local tissue region causing jacksonian seizures, hemianopsia, and so on. Chelation effects were doubtful in her first admission,[3] but during the second admission there was cessation of severe seizures which had occurred 12 or 13 times daily and had failed to respond to heavy anticonvulsant medication; again no distinct abnormal porphyrin excretion pattern could be demonstrated. Chelation seemed to bring about rapid recovery when it was ultimately instituted.

Chlorpromazine has been reported as an adjunct helpful in the control of acute porphyria.[34,35] We have observed patients with severe side effects from only small amounts of chlorpromazine,[3] while in others we have used this drug with some benefit during minor exacerbations of abdominal colic. In a case reported by Seide there was a fatal result, despite chlorpromazine administration throughout the course of the illness. Since chlorpromazine may cause an increase in copper excretion,[36] its value may be related to a minor chelating effect.

CASE REPORTS

Case 1. A white female, age 62, was admitted to the University Hospitals on December 31, 1957, with complaints of intermittent pink urine, a 20-pound weight loss, insomnia, and fatigue of six to seven weeks' duration. There had been recurrent flatulence and dyspepsia, especially severe at night, and she had required nocturnal sedation in order to sleep. The patient gave a 20-year history of recurrent abdominal bloating related to ingestion of fried foods, gravies, beans and pork, and unassociated with jaundice, nausea, vomiting, or acholic stools. Oil-based paint was used frequently by the patient. She had had a D and C in 1953 for cervical polyp and a bilateral saphenous ligation in 1951. The family history was essentially negative.

On neurologic examination, she appeared to be an anxious woman and phobic trends were noted in her psychiatric inventory. There was diffuse melanosis of the face, chest, and arms, with freckling and erythema of midforehead and malar prominences. Several keratoses over the arms were noted. Cranial nerves were intact, except for slight anisocoria. Deep tendon reflexes were equal and active and plantar response was flexor.

Serum proteins were 8.1 gm. per cent, albumin 4.9 gm., globulin 3.2 gm., bilirubin 0.6 mg. per cent, and direct bilirubin 0.2 mg. per cent. Routine urinalysis and hemogram were within normal limits. Prothrombin time, hematocrit, fasting blood sugar, and nonprotein nitrogen were normal. Sedimentation rate (Wintrobe tube) was 22 mm. and alkaline-phosphatase 16.3 units (King-Armstrong). The cerebrospinal fluid was negative and spinal fluid pressure normal. Urinary tests for coproporphyrin were 5 plus, uroporphyrin 5 plus, delta-amino levulinic acid 2 mg./l., and porphobilinogen 0.4 mg./l. Fecal protoporphyrin was 10 plus (markedly abnormal). Urinary zinc excretion was 0.55 mg. per liter, lead negative, and copper 0.3 mg. per liter (six times normal). The electroencephalogram was negative and a chest roentgenogram revealed only a calcified primary complex on the right. Bromsulfalein retention was 22 per cent in 45 minutes.

Course in hospital. During hospitalization the patient complained of increasing restlessness and anxiety. She slept poorly at night. On January 15 BAL therapy was instituted, 0.5 cc. three times a day. The following morning the patient stated that she had been able to sleep through the previous night and that her anxiety was greatly improved. Recovery dated from that time. After ten days of treatment she was discharged on a maintenance program of 1 cc. of BAL intramuscularly daily. When seen in the outpatient department she stated that she was feeling extremely well and gaining weight. Phobic symptomatology had vanished. She was continued on oral disodium EDTA 0.5 gm. three times daily and seen monthly in the outpatient department. Objectively the patient appears less darkly pigmented. Follow-up tests on the patient's urinary copper and zinc excretion revealed an increase in urinary copper excretion after the institution of BAL.

We consider that this patient represents a mixed hepatic porphyric with both cutaneous and psychiatric symptoms. As with four other mixed and one chronic porphyric patients, urinary copper excretion was elevated during exacerbation and prior to chelation. BAL induced more copper diuresis and symptoms responded favorably.

Case 2. A 27 year old housewife was admitted to University Hospitals on November 5, 1954. The illness began in 1949 and was characterized by right frontal headache, high fever, nausea, unconsciousness, and grand mal seizures. The latter occurred repetitively as many as 34 seizures in two weeks and were followed by left hemiplegia. Within three weeks the patient's seizures and paralysis cleared completely. Six months later a similar episode occurred requiring hospitalization. Three weeks prior to the current admission, repetitive jacksonian seizures occurred. These were characterized by an aura of "a ball of fire" and

"something pulling on the right side of the head" and involved the left upper extremity. They were usually accompanied by urinary incontinence and tongue biting. She was hospitalized elsewhere before admission to this hospital and received treatment injections to control the grand mal seizures. It is assumed that these were sedative and anticonvulsant drugs. She had been disoriented and emotionally labile and complained of blurred vision.

Upon admission the patient was found to be oriented but lethargic. She complained of recurrent dull aching pain in the flanks. There was tenderness to palpation in the lower abdomen, the lumbar area, buttocks, and the extremities. She was hallucinating, both in the visual and auditory spheres. She expressed the fear of dying and reported a series of kitchen cabinets passing through her field of vision. Left homonomous hemianopsia was present and there was weakness of the left hand. Hypertrophy of the gums was noted. Otherwise the neurologic examination was not remarkable.

The family history and past medical history revealed that the patient's mother and three sisters had diabetes mellitus. The husband stated that she had been taking a white powder for headaches, the nature of which was unknown since no specimens of this medication were available for examination. The patient's husband was an interior decorator who frequently worked with paints and kept them around the house, as well.

Course in hospital and laboratory findings. The patient was treated with calcium versenate therapy, followed by nine days of BAL treatment because of the finding of abnormal amounts of arsenic in the urine (10 microgm. per liter), the hair (8.26 microgm. per gram), and in the proximal hair (17.3 microgm. per gram). Arsenic in the fingernails was negative. During this period of chelating treatment the patient developed thrombophlebitis and it was also evident that she was three months pregnant. Because of continuing psychotic behavior, electroshock therapy was instituted. Following the second electroshock treatment, the patient developed emesis and marked confusion. Three grains of sodium Amytal was administered in the postictal phase, because of excitement following the first two treatments. The following day she was semistuporous, the eyes drifted to the left, and there was increased tone of the right upper and lower extremity, with hyperactive reflexes in all extremities, more so on the left than on the right. Right-sided jacksonian seizures commenced and continued, despite use of paraldehyde. A left temporal frontal focus was suspected. Electroencephalographic examination upon admission had been normal, but on January 8, 1955 there were many one to two per second 100 to 150 microvolt waves lateralizing to the left cerebral hemisphere. Jacksonian seizures continued repeatedly over the next four days and finally extended into generalized seizures. On some days she had as many as 32 grand mal seizures in a 24-hour period.

A pneumoencephalogram was performed on January 12, 1955 under Avertin anesthesia. There was no evidene of a space-occupying lesion. Following the pneumoencephalogram, seizure activity continued. At this point BAL therapy was instituted and the seizures subsided in frequency. There was a gradual improvement in the patient's condition and by February 28, 1955, she could ambulate without assistance. There was continuing evidence of psychosis, however.

Urinary excretion of porphobilinogen and uroporphyrin had been negative. The coproporphyrin levels ranged from 3 to 5 plus. On January 4, however, the urine for the first time revealed positive Watson-Schwartz reaction and this was true on a repeat determination on January 17, 1955. Thereafter this test was intermittently positive on several occasions and uroporphyrin was identified in the urine on March 25, 1955.

On March 4, 1955 she again developed left homonomous hemianopsia and slight hyperreflexia of the left upper extremities. This was followed by emesis and later a left hemiparesis which cleared in several days. On March 7 she complained of right supraorbital pain and again had anisocoria. Three days later there were 13 jacksonian seizures involving the left upper and lower extremities. Dilantin was started, as well as BAL and phenobarbital. The seizures occurred intermittently throughout the following month and the psychotic symptoms were also quite evident. On May 15, 1955 she delivered a nine-pound normal female child. Fingernail and hair clippings of the baby were negative for arsenic. The postpartum course was smooth until June 16, when she again had a grand mal seizure followed by recurrent jacksonian seizures and left homonomous hemianopsia. BAL therapy was again initiated. The seizures subsided gradually following repeated injections of phenobarbital, rectal Avertin, and small doses of ACTH. The patient then developed atelectasis and a tracheotomy was performed. Because of the chronic psychotic state, Frenquel was tried on July 9, 1955, in doses of 20 mg. twice a day for three days. The patient seemed to improve. She was discharged on August 25, 1955, at which time an electroencephalogram was recorded as completely normal.

The patient was followed in the outpatient department the ensuing several years, and on two occasions porphobilinogen tests were positive on random samples of urine.

On December 20, 1957 she was re-admitted to the University Hospitals. Five days prior to admission the patient's husband had painted the living room. The day before admission the patient suddenly developed a right-sided jacksonian seizure, followed by deep coma. She was aphasic and manifested a conjugate deviation of the eyes to the left, with recurring jacksonian seizures of the right upper and lower extremities. There was right-sided hyperreflexia and a positive Babinski sign on the right foot. An electroencephalogram showed a left temporal parietal slow wave focus. The

spinal fluid examination revealed a protein of 50 mg., a low mid-zone gold sol curve, and normal cell count.

Coproporphyrin was 5 plus in the urine, the uroporphyrin was negative, and quantitative porphobilinogen and delta-amino levulinic acid were normal. Fecal protoporphyrin was negative.

High doses of phenobarbital and Dilantin were used to control the seizures, but they were ineffective. On December 27, 1957 the patient was given BAL therapy, with a prompt reduction in seizure activity. Seizures became grand mal in type. By December 30, 1957 the right hemiparesis showed marked improvement, she was more responsive, and seizures ceased. Atelectasis and pneumonitis again developed as a complication, and tracheotomy was performed. BAL was continued until January 27, 1958 and disodium calcium versenate was administered intravenously. Large sterile abscesses developed in both buttocks, requiring incision and drainage. There was gradual improvement in her intellectual function. On March 10, 1958 the patient was able to be discharged.

We feel that this case represents paraporphyria, possibly precipitated by exposure to toxic quantities of arsenic in the first instance and by exposure to oil-based paints in the second. The chronic psychotic reaction of this patient is of interest, and it is the impression of one of the authors that the patient's immediate relatives manifested borderline psychotic behavior also. During the first hospitalization her response to BAL therapy was considered equivocal. Frenquel was felt to be of assistance in improving the psychosis. During the second admission phenobarbital and Dilantin seemed to aggravate seizure activity or at least to be completely ineffectual. Initiation of BAL therapy on this occasion resulted in impressive improvement. The failure to find significantly abnormal disturbances in porphyrin urinary metabolites during the second admission is of interest and emphasizes the intermittency of porphobilinogen excretion and the failure of accurate correlation with clinical status. It is for cases such as this that we feel the term paraporphyria is useful.

Case 3. A 28 year old man was admitted to University Hospitals on February 21, 1956. Three months prior to admission he developed right lower quadrant pain, diarrhea, and emesis. An appendectomy was done under Pentothal anesthesia and the appendix was normal. Postoperatively he developed progressive weakness of the upper and lower extremities, cramping pain in the thigh, and a 40-pound weight loss.

The patient was the second of nine children and two other siblings are believed to be mentally ill. Past history discloses that the patient entered a seminary at age 18. He was transferred to a second seminary and at this time developed a paranoid illness with delusions concerning communists; on one occasion he had run away from the seminary in his night clothes and was jailed by the police. Following this he returned to his father's farm and worked there until the present illness.

Neurologic examination revealed hoarseness. There was marked weakness and atrophy of the shoulder girdle and moderate weakness of the distal muscles of the upper extremity. The triceps reflexes were absent and the biceps were reduced. There was moderate quadriceps, iliopsoas, and adductor weakness in the lower extremities, with preservation of patellar and Achilles reflexes. There were no pyramidal tract signs. There was decreased deep pain sensation in the Achilles tendon. Sensory examination was otherwise unremarkable.

Laboratory and roentgenographic findings were as follows: Biopsy of the deltoid muscle revealed dilated blood venules, with infiltration of lymphocytes and tissue phagocytes. The muscle fibers were decreased in size and the sarcolemma nuclei seemed closer together. The diagnostic impression was vasculitis, with mild muscular atrophy. The urine showed 5 plus coproporphyrin, 3 plus uroporphyrin, and positive porphobilinogen on Watson-Schwartz test. Urinary zinc and arsenic were normal on admission. There was no creatinuria. Hemogram, urinalysis, nonprotein nitrogen, chlorides, sodium, and potassium were normal. Carbon dioxide was 18 mEq./l.

Course in hospital. The patient remained quite withdrawn on the ward. His affect was flat. He did not socialize with other patients and made no attempts to initiate conversation. He was unable to dress himself and at times he was seen to smile inappropriately. A Rorschach examination two weeks after admission was compatible with a chronic schizophrenic reaction. Porphobilinogen, uroporphyrin, and coproporphyrin continued to be positive in the urine. On March 6 BAL therapy was initiated in a dosage of 0.7 cc. twice a day for ten days. After three doses of BAL the patient reported feeling stronger and speech became more spontaneous. At this point he admitted having experienced visual hallucinations in which locomotives ran through his room, as well as auditory hallucinations of people's voices. On March 9 he stated that his thinking was clear, the hallucinations were gone and he felt definitely stronger. It was observed that walking took place with less difficulty and he could now raise his upper extremities with slight difficulty. BAL was discontinued on March 16. On May 7, 1956 there was recurrence of abdominal pain and vomiting accompanied by an increase in porphobilinogen and delta-amino levulinic acid; zinc excretion increased to a level of 3.5 mg. per liter. BAL therapy was reinstituted on May 7, 1956, with immediate improvement in abdominal symptoms. During and

after chelation therapy there was consistent improvement in the patient's behavior, manifested by his participation in occupational therapies and social activities on the ward. By May 24, 1956 his muscular strength had largely returned. Follow-up reports indicated that one year later the patient was doing farm work and felt perfectly well. There is no evidence of psychiatric difficulties in a recent follow-up report.

This case is of particular interest because of the venous vasculitis reported on muscle biopsy. This has not been observed by us in other cases. We place this man in the porphyric-schizophrenic group, a type of hepatic acute porphyria. It is our impression that the psychiatric symptoms here showed marked improvement with BAL therapy. Unfortunately the patient's family was not cooperative and studies on them could not be carried out. However, there was a suggestion of a genetic basis from the family history.

Case 4. A 35 year old woman was admitted to University Hospitals on September 10, 1957. Her medical history dated to age 17 when an appendectomy and a uterine suspension were performed. Twenty cystograms were performed during the following two years because of pain in the right kidney area. Sulfa drugs at that time caused extreme stomach upset. At age 19 a partial hysterectomy was performed because of recurrent menorrhagia and dysmenorrhea. At age 23 an ovarian cyst was removed under spinal anesthesia, the patient having experienced severe low abdominal pain, accompanied by constipation and emesis in recurrent attacks. At age 24 surgery was performed for adhesions and displacement of the cecum, relieving right lower quadrant pain for five months. At age 25 she was in bed for five months with pain in the right lower quadrant, and her weight deteriorated to 90 pounds. Radiation therapy relieved what was thought to be reactivated endometriosis. The patient did well until age 28 when she developed asthma, for which recurrent bronchoscopy and submucus resection were performed. At age 30 cervical amputation was performed, as well as a D and C, because of recurrent menorrhagia, dysmenorrhea, and constipation. At age 34 her right knee was operated upon uneventfully for "joint mice."

The patient's work record had been spotty. A year before her present hospital admission she stopped working because of interpersonal difficulties with a new boss. During the previous ten years the patient had suffered migraine headaches, for which Ergotamine and Seconal had been prescribed. The suspicion was held that the patient was addicted. The father had been asthmatic, the mother had hay fever, and a maternal grandfather had history of recurrent abdominal colic and migraine headaches.

Because of recurrent right upper quadrant pain and roentgenographic evidence of a non-functioning gallbladder, hospitalization on September 10, 1957 had been arranged for possible surgery. The question of pancreatitis had been raised by frequent elevation of serum amylase, possibly due to use of narcotics. After admission to the hospital complaints of severe right upper quadrant pain persisted. On several occasions after administration of 100 mg. Thorazine the nurses found it very difficult to awaken her in the morning. At this time the patient mentioned recurrent syncopal attacks with confusional episodes in the last two years and described myoclonic-like jerking movements of the extremities. An electroencephalogram revealed generalized abnormality in the form of paroxysmal 300 microvolt three to five per second waves. Despite severe right upper quadrant pain, there was no fever, rigidity, guarding, mass or deep and rebound tenderness. Possible obstruction of the cystic duct was considered and surgery was performed on September 20, 1957. Postoperatively the patient was unable to sleep and her appearance suggested ethanolization, with red eyes and nose. Complaints of abdominal pain persisted.

On September 22, 1957 coproporphyrin values were 3 plus and uroporphyrin slightly positive. The following day the patient began accusing herself of having done non-Christian things and expressed ideas of hopelessness. She admitted hearing voices outside her room. Other people seemed to be "up higher than she was." Everything that she looked at assumed a pattern or mozaic, including the tree branches outside her window. The diagnosis of acute porphyria precipitated by preoperative Nembutal ingestion was made on the basis of the clinical picture, which included brawny tanning of the skin, as well as the psychosis. Though oriented as to place and time, her affect was minimal. Fecal protoporphyrin was frequently elevated during her hospital stay; we were unable to identify porphobilinogen but noted an increase in delta-amino levulinic acid amounting to 9.2 mg. per liter. Urinary copper and zinc likewise remained within normal limits. The patient was placed on Frenquel, 40 mg. four times a day, with resultant rapid recovery from psychotic symptoms.

The patient's course following discharge from the hospital included recurrent abdominal pain, at times precipitated by Seconal which she used despite contrary advice. On all occasions hospitalization in her home town and use of intravenous EDTA seemed helpful in bringing about recovery. During these later hospitalizations elsewhere, her local doctor noted that the Watson-Schwartz test was positive, whereas positive values were not obtained in the initial hospitalization. Arrangements were made for a psychotherapeutic program in this patient who displayed evidence of emotional immaturity, as well as some hysterical features. The presence of addiction, in our opinion, gravely alters the ultimate prognosis.

In summary, this patient represents a typical pattern of frequent surgical procedures, with the development of considerable dependence on opiates and barbiturate drugs. The history includes recurrent and abdominal pain which did not respond to surgical or ordinary medical measures. There was evidence of a psychiatric disability of grave proportions. In this case there seemed to be a clear relationship between the precipitation of acute episodes and the ingestion of barbiturates. Therefore, we consider this case as one of acute hepatic porphyria of the intermittent type. Despite the initial failure to demonstrate porphobilinogen in the urine, all other features of the case, including a later demonstration of porphobilinogen, are typical. It is our opinion that the presence of addiction, under such circumstances, is a grave prognostic factor.

SUMMARY

Symptoms and signs of 48 porphyric patients, including five mixed and one chronic porphyric, are summarized. Eight of these patients had suggestive clinical symptomatology, with increased fecal protoporphyrin excretion, elevation of delta-amino levulinic acid, and increased urinary zinc and/or copper. They are thought to be related to acute porphyria and the term paraporphyria is suggested. Elevation of urinary copper was present in four mixed and one chronic hepatic porphyric patients. Symptoms of porphyria are thought to be due to a zinc, copper, or other cation block of several metallo-enzyme systems. Exhaustion of certain portions of the body's natural chelation defenses and subsequent depletion of porphyrins for purposes of chelation may likewise impoverish the metabolism of the body and affect the maintenance of myelin and the cytochrome systems that interrelate to a "porphyrin pool." Artificial chelation is felt to replenish the depleted chelation reserves of the body, thus restoring more normal metabolism.

Chelation therapy with BAL or EDTA seemed helpful in 31 of 37 patients, including eight paraporphyrics and five mixed hepatic porphyrics. An identical tryptophan excretion pattern was recorded in most acute, mixed, chronic, and paraporphyrics studied. Included is a concept of the porphyric-schizophrenic who shares the same metabolic error and is helped by chelation. Complete recovery from tetraplegia due to porphyric motor neuropathy does occur but may take as long as a year.

Maximal nursing care; tracheotomy; attention to electrolyte balance; avoidance of barbiturates, sunbathing, steroids, and heavy metals; and physical therapy are essential.

We are indebted to Dr. F. L. Kozelka and Mrs. Wanda M. McCarty for their invaluable guidance and assistance in this study.

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■ The attack of apoplexy is sometimes sudden; sometimes we are warned of its approach by the following symptoms: a dull pain in the head, accompanied by a sense of weight or heaviness; vertigo; drowsiness; frequent fits of incubus; involuntary contractions of the muscles of the face; cramps or spasms in various parts of the body; inspirations deeper than natural; fulness and redness of the countenance and eyes; obscurity or irregularity of vision; bleeding from the nose; ringing in the ears; faltering in speech, or using one word for another; loss of memory; and diminished sensibility of body or mind, or of both.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Treatment of heredodegenerative disorders

A continuing challenge to neurology

Walter O. Klingman, M.D.

It is with great personal pleasure that the officers and members of the Board of Trustees of the American Academy of Neurology welcome you here in Boston where so many of the membership have had their introduction to the field of neurology under numerous able and outstanding men. The attendance at this meeting, the scope and volume of the program presentations, the enrollment in the special courses conducted prior to the scientific meeting, and the number and caliber of scientific exhibits and demonstrations all bear witness to the fact that this Academy has progressed well beyond its organization period.

The American Academy of Neurology is now faced with the need of providing for development and expansion in a careful and considerate fashion, keeping our aims and goals in mind, being realistic and perhaps venturesome at times, and evaluating the increasing demands of a rapidly expanding organization.

This is the first meeting where a section activity of the Academy is included. In less than a year's time the Section on Neurochemistry has reached a point far beyond expectation. Furthermore, the large number of presentations that warranted program participation has made it necessary for the program committee to schedule scientific sessions operating concurrently. These features of the 1957 meeting undoubtedly represent the total needs of a rapidly expanding membership and also reflect the increasing importance of the role that neurology is playing in American medicine. Not only is this true of neurology in this country, but also of neurology the world over, judged by the growth in distribution of *NEUROLOGY*, the official journal of the American Academy of Neurology, to all parts of the globe.

This progress seems to vindicate the vision and hopes of the founders of the Academy. No doubt, it also creates some consternation among a few of the membership who may prefer restriction of these activities. However, we must meet the demands of the times realistically and be experimentalists sufficient to lead this developmental phase with well maintained guidance and control. The membership must have confidence and faith in the officers and trustees to guide this expansion of activity and to assure that this progress continues.

This preamble leads in a fitting manner to the topic of my address to you. It consists of a preliminary report of a venturesome experiment, but at the same time it expresses a cautious, experimentalist approach similar to that which faces the Academy in its expansion. In this instance, it represents a two-year venture in a therapeutic approach to the continuing problem and need of therapy for a large segment of neurologic disorders, the degenerative disorders, for which in the past we have had little to offer beyond recognition of the disorder.

In this two-year venture, observations made in the course of investigations of disorders of other character, in which metabolite deficiencies occurred, offered sufficient background to study some of the degenerative disorders. From it has emerged unanticipated degrees of change sufficient to encourage further efforts

From the Univeristy of Texas Medical Branch, Galveston, Texas.

Presidential address delivered at the ninth annual meeting of the American Academy of Neurology, Boston, April 24, 1957.

toward more specific therapy, as well as determination of etiology and pathogenesis as it applies to some of the so-called degenerative disorders of the nervous system, with or without the hereditary consideration. In this study a selection of two degenerative groups was made, the nuclear amyotrophies and muscular dystrophy. The selection was based upon degenerative and hereditary features that both present, particularly because of similarities in metabolic failure.

The nuclear amyotrophies represent a large group of clinical syndromes, depending upon location of the nuclear changes. They include such disorders as progressive muscular atrophy, the infantile forms of spinal muscular atrophy of Werdnig-Hoffmann and of amyotonia congenita of Oppenheim, amyotrophic lateral sclerosis, primary hereditary ataxia, progressive bulbar palsy, progressive chronic ophthalmoplegia, familial spastic paralysis, and Charcot-Marie-Tooth peroneal atrophy. The other group, considered under the myopathies, was progressive muscular dystrophy.

These disorders are characterized by two features. One is the early breakdown or degeneration of ganglion cells, such as occurs in the nuclear amyotrophies, and faulty development or early breakdown of muscle tissue, which is seen in the myopathy group. The second feature in practically all of these disorders is the high incidence of a genetic factor, manifesting itself as a familial disorder or being transmitted from generation to generation, sex-linked in some instances, recessive or dominant in the mode of transmission in others. Another common feature that these disorders display is evidence of faulty or immature tissue development in infancy or even in the intrauterine period, or faulty breakdown of ganglion cells or muscle cells occurring after what appears to be a normal state of health for many years after birth.

Our particular interest in these categories of disorders was aroused by studies relating to the role that ions or electrolytes play in metabolic or enzymatic activity associated with the paroxysmal disorders. In these investigations we became more and more aware of the role that certain ions play in metabolic activity of neuronal and other tissue. In recent years we have been impressed by the role that magnesium played in metabolic derangements and have already reported on clinical features associated with magnesium depletion states.[1] In this, our attention was attracted by the alterations of nerve-muscle unit activity in which magnesium seemed to have a relation to tremors, muscle twitchings and jerkings, weakness, and ataxia, aside from actual seizures states, states of clouded consciousness, or toxic exhaustion psychotic manifestations.

In reviewing our studies, it appeared that influencing nerve and muscle function in such disorders as the nuclear amyotrophies and dystrophies might conceivably alter or overcome defects which existed in these disorders due to lack, deficiency, or inability to metabolize critical ingredients or metabolites. Possibly the derangement of metabolic disorder might be corrected, reversed, or stabilized by supplying necessary enzymatic or other biochemical factors similar to those encountered in magnesium depletion states. We also assumed the presence of an inherent, genetic factor in these altered metabolic states. In the previous studies, magnesium seemed to play a necessary role in the completion of biochemical functions in both nerve and muscle tissue. Furthermore, the metabolic role of magnesium and other ions appeared to have some relation to the gene factor present in heredodegenerative disorders.

Such a concept should not be so unusual, in view of our present recognition of the important role that specific vitamins play in the nervous system in deficiency states, such as pellagra, beriberi, and the anemias where there may not only be a true deficiency, but where restoration and maintenance of certain nerve cells and pathways depend upon a continuing supply of many times the normal concentration of a metabolite.

By a somewhat similar but a differing mechanism, there has been a growing approach to another nervous system disorder, hepatolenticular degeneration or Wilson's disease, which gives evidence of linkage with abnormal copper metabolism and other metabolic defects. In this disorder, there is impairment of normal blood serum ability to bind copper, presumably by a plasma protein constituent, ceruloplasmin, due to a deficiency of this particular plasma protein. As a result, there is

too much free or unbound copper present in the blood and urine. Just how these factors enter into production of the lesion is not well understood. Yet the copper and amino acid metabolic derangement in Wilson's disease seems quite definitely characteristic in the affected individuals and often in others of the family.[2]

Inasmuch as nerve cell biochemical processes are intimately related to the proper function of intracellular enzyme systems, which usually require a step-by-step completion of their biochemical assignment in normal cell life, failure to carry these processes through to metabolic completion seems to offer many opportunities where intracellular activity might be altered or break down. The biochemical processes are not necessarily confined to intracellular activities, but may also be critical for tissue membrane or extracellular activity.

Nucleoprotein activity and phosphorylation stand out as prominent factors in nerve cell activity. What is known of genes is that they are complex nucleoproteins having the properties of self duplication and ability to mutate or to alter biochemical activity. Present day concepts, supported by strong suggestive evidence, indicate that genes direct development and other functions intimately related with the biochemical activities of the organism during embryonic development, or even if development seemingly has reached a normal or complete state.[3] Preliminary deductions regarding muscular dystrophies seem to indicate that one is dealing with a disorder which, in all likelihood, is a congenital defect rather than a degenerative change later than that occurring after embryonic life.[4]

Recent experimental work on gene activity indicates that a biochemical factor is responsible for producing differentiation of cells. The factor identified in living tissue is ribonucleic acid. In further experimentation this factor was proved to have the ability to initiate cell differentiation if ATP (adenosine triphosphate) was added. Tagged ribonucleic acid protein was shown to be taken up by the differentiating cells. This suggests that specific types of ribonucleic acid may be the inducers of specific proteins, particularly enzymes, which make cell types differ from each other. There are additional clues that, as tissues differentiate and mature in the embryo, they may elaborate substances which have the ability to inhibit their still undifferentiated cells from following in the same pathway of specialization.[3]

In this fashion there seems to be a very intimate relation with biologic activities, once the organism tissue becomes complete and is apparently normal. However, the gene direction of biochemical activities or future biochemical activities and events results in altered biochemical states. This reduced or altered relationship results in misdirected activity and the result is a so-called degenerative disorder. Gene activity may also be responsible for electrolyte or ion disorder involved in metabolism. An example of this is found in familial periodic paralysis, a dominant hereditary affliction due to a potassium metabolic disorder. In some instances of this disorder there may also be muscular atrophy, in addition to episodes of transient paralysis.

Such recognized biochemical abnormalities due to genetic mechanisms are thought to cause specific effects which will result in abnormalities, such as an abnormal binding of potassium in family periodic paralysis or, in hepatolenticular degeneration where a deficiency may exist in a particular protein's ability to bind copper, aside from an alteration which influences the kidney threshold for certain amino acids.

Therefore, considerable seems to be known or observed or postulated for such conditions that permit one also to apply these concepts to other hereditary disorders or degenerative diseases as they affect nerve or muscle tissue, such as in the nuclear amyotrophies or in the myopathies. In the dystrophy group one may actually be dealing with a congenital defect which later in life is manifested as a tissue metabolic alteration or breakdown or degeneration. This same characteristic may well apply to some of the other hereditary degenerative disorders of the nervous or muscular systems, whereas formerly this feature was explained on the basis of abiotrophy.

In a somewhat similar light, we understand better how exogenous toxins, such as arsenic, influence nervous system metabolic activity by a blocking effect or competition for a critical substance necessary to maintain normal neural

structure activity; as a result, a degenerative change in the nature of a neuropathy occurs.[5]

At a previous Academy meeting, a new kind of attack on epilepsy was launched upon findings suspecting a basic defect in body chemistry, with the hope that regular intake of ingredients would lead to the correction of a metabolic defect and control of epilepsy by maintaining and adequate intake and maintaining in nerve cells two important biochemicals, glutamine and asparagine. In these efforts was represented the contribution of amino acids for utilization of a supply of energy for the deficient nerve cell in the hope that this would influence a biochemical lesion in the brain that causes epilepsy. By correcting a deficit of critical ingredients found in nerve cells in areas from which seizures were arising, it was hoped that control of convulsions by such means might be obtained, rather than by medications which function by depressing nerve cell activity. The biochemicals would, in this sense, assist in replacing specific nerve cell deficiency that leads to convulsions.[6]

We were particularly impressed by the role that ions played in metabolic processes. Inasmuch as one of our interests originally concerned magnesium, we began to interest ourselves even more in its relationship to other metabolites or the combinations with other metabolites that might constitute critical factors in maintaining healthy nerve or muscle cell activity. The fact that many enzymatic reactions were accelerated by sufficient presence of certain ions, or where completion of biochemical processes did not occur except in the presence of certain ions or other metabolites, led to evaluation of the effects of supplying ingredients to individuals who had degenerative nervous system disease. Important in the functioning of nerve and muscle cells seemed to be two major ones, whereby favorable utilization of carbohydrate metabolism and the adenylic system might indicate that critical ingredients involved might also provide key metabolites to restoration and maintenance of function, provided tissue changes had not already reached irreversible stages.

In this evaluation it became apparent that, in the process of the breakdown of glucose, high energy phosphate bonds were created as a result of the adenylic system activity. In this it also became apparent that the adenylic system participated in vitamin action and likewise provided energy for muscle contraction and relaxation. The universal source of the immediate energy for activity of nerve and muscle tissue, as well as other tissues, was adenosine triphosphate (ATP). It also entered into the activities that pertain to nerve impulse conduction, contractility of muscle, and secretion. Considered important by many investigators is its relationship to the processes whereby production of acetylcholine affects nervous tissue. It had already been recognized that the action of ATP was markedly potentiated by the administration of magnesium. It had also been shown that in muscle glycolysis some phosphate group transference was accelerated by sufficient presence of magnesium and cobalt ions and other ions.[7]

Elaborate metabolic processes are present in carbohydrate breakdown, and the presence of certain metabolites is necessary for the completion of the metabolic reaction. These include, among others, adenylic acid (precursor of ATP), magnesium or manganese ions, and thiamine and methionine. Other enzymes involved in muscle phosphorylation are the phosphokinases. These all have the common property of requiring the presence of magnesium. Thiamine is one of the phosphokinases. ATP also plays a role in formation of creatine, which could be important in muscle metabolism in that creatine phosphate present in muscle acts as a reservoir of available energy. In the phosphate energy reactions a dependency could exist upon the concentration of an ion, magnesium, to form the complexes relating to ATP, and, conceivably, this might be an important factor. In the complete absence of magnesium the enzyme factor has been known to remain inactive.

Person in 1955[8] had postulated that in progressive muscular dystrophy there was an inherited or acquired derangement in the combination between the iron-actomyosin and ATP which causes muscle contraction. An explanation for the reduction in creatine in progressive muscular dystrophy was secondary to reduced or available ATP, according to his concept. He likewise referred to the need for presence of iron for the phosphorus uptake of actomyosin and indicated that a part of the iron in muscle

is in an as yet unknown type of combination with the actomyosin. Szent-Gyorgi[9] could initiate muscle contraction with the action of ATP. He further reported that Reinhold and Kingsley[10] contended that there is a reduction of the absolute quantity of ATP per gram of muscle in muscular dystrophy. Person felt that, in the final analysis, the creatine and phosphocreatine disappear more quickly than the ATP; he felt that the essential factor was the reduced total content of ATP in muscle and that active muscle is replaced by fat and connective tissue eventually as a result of these alterations.

Nerve and muscle tissue have factors of metabolic importance in common in their metabolic activities. In the nuclear amyotrophies, as well as in muscular dystrophy, progressive muscular atrophy, amyotonia congenita, and very likely also myasthenia gravis, lack of derangement of proper metabolic activities is under suspicion. Detecting the key defects in these abnormal metabolic processes or derangements offers some clue, leading to a correction of the biochemical lesion or proper maintenance or sustained physiologic function by such correction. These may involve processes intimately related to intracellular enzyme systems or cell surface or membrane activities. Many of the disorders have genetic factors involved, suspected as being nucleoproteins in nature. Carbohydrate glycolysis and nucleoprotein linkage in phosphorylation necessary for proper nerve-muscle function seem to be well established.

Because of these considerations and because time does not permit us to go into the complexities of the involved biochemical factors, our interest in key metabolites and ion activity led to an effort over a two-year period to note changes occurring in hereditary degenerative disorders by supplying some of the involved metabolites, making more ATP available, catalyzing phosphorylation, and influencing energy transfer exchanges which govern physiologic processes in which carbohydrates, nucleotides, and ions are involved. This has resulted in most encouraging clinical responses. The role of magnesium was respected, but it was difficult to find a magnesium salt which would be assimilated until magnesium gluconate was found to have such property. The most active phosphorylation needs are known to exist in brain tissue as well as in muscle tissue. Supplying added sources to contribute to improvement of function of nerve and muscle tissue was attempted by the administration of 1) adenylic acid in the form of adenosine-5-monophosphate, commercially available as My-B-Den; 2) thiamine hydrochloride orally, or Beta-methiscol, for its thiamine, methionine, and choline content; and 3) magnesium gluconate. Choline was felt to be desirable for muscle metabolism. These were given in the following manner: My-B-Den (sustained action form) was given in a 1 cc. intramuscular injection in the gluteal muscles three times per week. Thiamine was given as a single 100 mg. dose orally each day, or Beta-methiscol was given in 1 tablespoonful amounts three times daily. Magnesium gluconate was given in 250 mg. tablet form three times daily. A rectal suppository form of My-B-Den has also been made available for use in young children. Its effectiveness in maintaining blood ATP levels, however, is only approximately 45 to 50 per cent as efficient as giving My-B-Den by the intramuscular method.

The accompanying tables are self-explanatory. Table 2 shows the blood and magnesium serum levels of patients who have been on the treatment program, as well as some untreated cases.

Over 100 cases of nuclear amyotrophy and muscular dystrophy have been observed for the effect of the therapy approach outlined. The most surprising in respect to improving

TABLE 1
INCREASE IN BLOOD ATP — MG. PER CENT

	50 mg. My-B-Den	*50 mg. My-B-Den with Mg. Cl_2*		*300 mg. Magnesium gluconate*	*50 mg. My-B-Den with 300 mg. Magnesium gluconate*
	0.1	0.3		0.9	1.1
	0.5	0.6		0.6	0.8
	0.0	0.4		0.6	1.2
	0.2	0.1		0.3	1.1
KC	0.1	0.2		0.7	1.3
	0.2	1.0	BB	1.2	0.5
	0.0	0.6		0.5	1.2
LK	0.2	0.4		0.3	0.0
BB	0.0	0.1		0.9	0.4
	0.0	0.5	LK	0.4	0.7
				0.0	0.0
			KC	0.9	0.0

TABLE 2

Name	*Dx*	*Magnesium*	*AA*	*ADP*	*ATP*	*Total Purine*	
C.U.	MS	1.69	0	0	5.9	11	T
M.D.G.	ALS	1.73	0	0	7.2	18.7	B-M
P.H.W.	CMT	1.73	0	0	5.2	13.3	T
G.H.	CMT	1.73	0	0	6.4	11.2	T
H.R.	MY	2.30	0	0	4.9	19.0	O(U)
S.F.	MD	1.69	0	0	7.8	16.1	T
J.S.	MD	1.56	0	0	3.0	10.9	O(U)
G.F.	MS	2.15	0	0	5.4	8.9	T
R.B.	MD	1.64	0	0	4.9	7.8	O(U)
B.K.	HA	1.64	0	0	5.4	13	B-M
R.D.	HA	1.52	0	0	6.4	9.6	B-M
B.S.N.	ALS	1.89	0	0	8.0	14.3	B-M

Attention is called to the elevation in blood ATP and total purine levels in this series receiving ASMP (My-B-Den), magnesium gluconate, and either thiamine or Beta-methiscol. Table 1 shows the striking differences obtained by various combinations and dosage of My-B-Den and magnesium chloride or magnesium gluconate, but without either thiamine or Beta-methiscol. The cases marked U were cases of neuromuscular disorders receiving other medications. The ATP levels are in mg. per cent. The cases receiving thiamine are designated by T and those receiving Beta-methiscol are designated B-M.

or maintaining function has been the muscular dystrophy group. Amyotrophic lateral sclerosis likewise has presented clinical courses not usually observed in untreated or empirically treated cases. Several in this group have made apparent dramatic recovery but also have given evidence of continued need of supportive or maintenance courses at intervals when indications of recurring signs or symptoms appear. In the group of nuclear amyotrophies have been included cases of family hereditary cerebellar ataxia and Friedreich's ataxia with variants, such as ophthalmoplegia, where improving function has been noted. One case of nuclear amyotrophy with bulbar involvement of severe degree with difficulty in deglutition, swallowing, and saliva control, intrinsic muscle atrophy of the tongue, and weakness of the erector capitis groups showed progressive improvement to the extent that the patient requested permission to return to his former full-time occupation.

Approximately 25 to 30 per cent of the cases continued to have a progressive downhill course, and it may well be that other key metabolites are involved. Also, at the beginning of our study, cases were included regardless of the stage or phase or duration of the disorder. It would be unnecessary to state that, if any influence was brought to bear upon these states, already irreversible changes would not be altered. In the latter period of study, cases were selected in the early stages of the disorder but where the clinical and other findings were in support of the diagnosis. In a number of instances, however, trial periods were given in advanced cases, purely because of the humanitarian aspects of the care and management of such cases. The decision of trying out the proposed therapy was left to the patient and the family, both being fully acquainted with the fact that it was a therapeutic trial.

Work in continuation of this approach is being carried on, considering other defects that may be responsible. Improved tissue and fluid assay methods, neural and muscle tissue culture, and model observations give promise of help in determining factors to be taken into consideration. Precursors and other bases are also being studied for evidence of deficiency or intermediary interruption of their biochemical or metabolic assignment.

The information presented must not be misconstrued as something equivalent to a cure. It is presented in the nature of preliminary observations upon the effects of the course of some degenerative disorders over a two-year period. It could well be that merely making more ATP available will only sustain or assist function temporarily and that actual correction of the degenerative process may require other assistance.

This paper is in the nature of a preliminary report in respect to meeting a continuing challenge that is presented in neurology by the

hereditary degenerative disorders. An experimental approach to such problems has been presented, with the underlying postulates. It is our hope that, with the enthusiasm and interest which this Academy has provided, the potentialities of unraveling the mysteries of so many disabling nervous system disorders can be realized by many in this organization, through the concerted effort of neurophysiologists, neuropathologists, neuropharmacologists, chemists, and the venturesome experimentalists. Nihilism should have no place in this organization. Neurology cannot afford to remain static in regard to these disorders.

Acknowledgment is made of support for this effort from the National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Maryland, The Ames Company of Elkhart, Indiana, Merrell Company of Cincinnati, Ohio, and the personal assistance and biochemical consultation services of Dr. Harry Albaum, Brooklyn, New York, in the analyses of serum studies.

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■ Epilepsy varies not only as to its form and degree, but as to the duration of the paroxysms, and the time of its return. Accounts of great varieties in these respects, might be adduced from numerous authors. The fits may last for a few seconds or minutes, or for many hours. In the case of a girl twenty years of age, the paroxysms, though not very strong, always lasted for fourteen hours. The ordinary duration of these attacks, is from ten to twenty minutes, when, the disease having arrived at its height, the respiration becomes more slow and easy, and the other symptoms disappear.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Excitability in experimental myopathy

1. Measurement of refractory period; quinidine effect; cortisone myopathy

Gilbert H. Glaser, M.D. and Lawrence Stark, M.D.

THE WIDE GROUP of myopathies includes natural diseases such as progressive muscular dystrophy, myotonic dystrophy, and polymyositis and a number of metabolic disorders often capable of being induced experimentally by such mechanisms as vitamin E deficiency, administration of cortisone, and potassium depletion. Definition of the effect of these pathologic states on the excitability of muscle is important, and the present investigation is an attempt to study this, utilizing a method of measuring refractory period. Refractory period, or time necessary for recovery between stimuli, is a fundamental property of irritable tissue. It was preferred for this study over such measurements as threshold, strength duration curve, or chronaxie, since it is based on maximal responses, as contrasted with minimal responses utilized in the other measures. These considerations led to the development of a method for measuring refractory period which is applicable to both human and animal investigations.[1]

METHOD

The experiments were performed using a series of young rabbits ranging in weight between 1.0 and 2.0 kg. In all instances the paravertebral muscles were studied, since they could be approached readily by the percutaneous route without disturbing the animal. All of the experiments were carried out with the animal in an unanesthetized state.

The apparatus consisted of a double-beam cathode-ray oscilloscope with amplifiers, timing signals, and calibrators. Two stimulators were utilized in tandem, producing double square pulses independently variable in duration, amplitude, and time interval. Bipolar stimuli were delivered through paired single electrodes, and recording electrodes were either coaxial needles or closely approximated pairs of single needles. Usually the needles were insulated except for the tips. Strength of stimulus was adjusted to a suprathreshold level for the muscle fasciculus adjacent to the needle, which was subthreshold for distant fasciculi. In this way it was found that a consistent maximal response could be obtained for this fasciculus. Measurements then were made of responses to two stimuli distantly spaced in time. The first action potential response was always maximal to the suprathreshold stimulus. The second action potential, initially equal to the first, was then reduced in amplitude due to relative refractoriness, as the time delay between the two stimuli was decreased (figure 1). Probably the main route of stimulation to the fasciculus is via the intramuscular motor nerves since these have a lower threshold than the muscle fibers. The refractory period of these nerves would be shorter than that of the muscle fibers.[2] Neuromuscular transmission at the endplate, not being all-or-none, does not show the phenomenon of refractory period, although it may contribute to the duration of the period by a factor of attenuation.[2] The actual refractory period measured by this method would appear to be that of the muscle fibers themselves, the longest in duration in this neuromotor system. For each experiment, change in excitability was plotted in terms of responsiveness to the second stimulus (figure 2). This responsiveness was determined as percentage of amplitude of the second action potential, as compared with the first. The measurements are considered to be self-controlled in that a full response from an excit-

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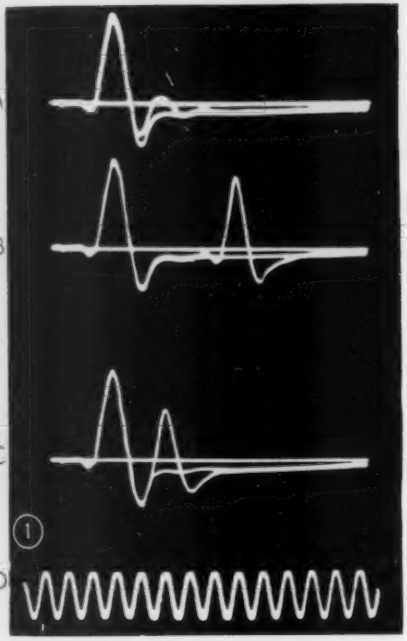


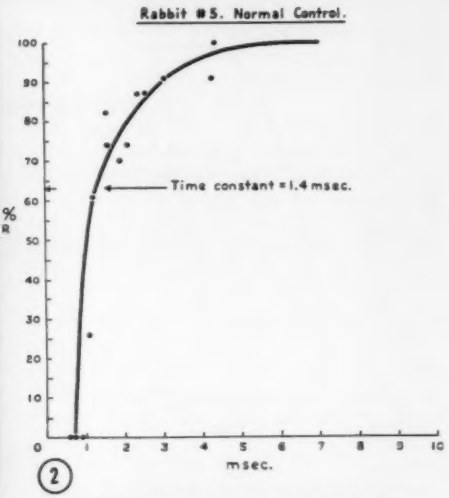


FIG. 1. Measurement of refractory period of paravertebral muscle of normal rabbit. *A*. Action potential at or near absolute refractory period. Minimal response to second stimulus. *B* and *C*. Action potentials in relative refractory period. Diminished responses to second stimulus. *D*. Time calibration at 1,000 cycles per second.

FIG. 2. Recovery curve of excitability in normal paravertebral muscle of rabbit. %R represents percentage of amplitude of second action potential as compared with the first. Abscissa in milliseconds represents time delay between stimuli determined experimentally.

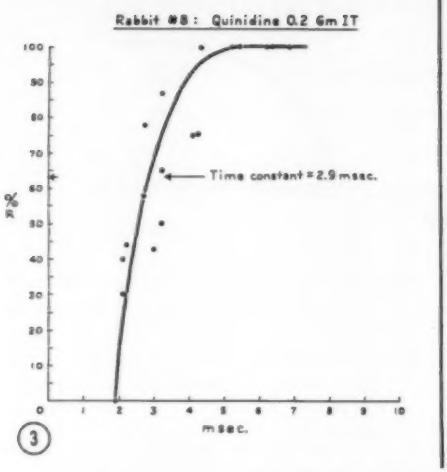
able tissue is compared with varying responses from the same tissue within a period of a few milliseconds. It was found that the midportion of the recovery curve appeared to be least variable, and a "time constant" was utilized as the measurement most descriptive of the curve. The absolute refractory period can be noted as the lowest point on the recovery curve, that is, the time at which there was no response to the second stimulus.

A statement should be made concerning the use of the "time constant." The recovery of responsiveness is really more complex than can be represented by a simple exponential curve. The actual measurement of absolute refractory period is somewhat uncertain, because it depends on the appearance or disappearance of a second response. However, the time of this period should be included in a single parameter intended to describe the recovery of responsiveness. Since the time constant is defined as the time taken for the amount of responsiveness to reach 63 per cent of full value, both the times of absolute refractory period and a less variable portion of the relative refractory period are included. It is felt that this represents a useful way of summarizing the structure of the entire curve.

EXPERIMENTS AND RESULTS

Control observations were made in 12 rabbits. The time constant of the recovery curve was determined to be 1.6 ± 0.1 millisecond, of which the absolute refractory period comprised about 0.8 msec. A typical experiment and response curve are presented in figures 1 and 2.

In order to check the applicability of this method in association with an action known to change striated muscle refractory period, quinidine was administered to ten rabbits. Quinidine was used in preference to quinine, since it was readily available in solution for parenteral administration. The dosage was varied in order to obtain an effect, but generally a dose of 0.2 gm. of quinidine gluconate



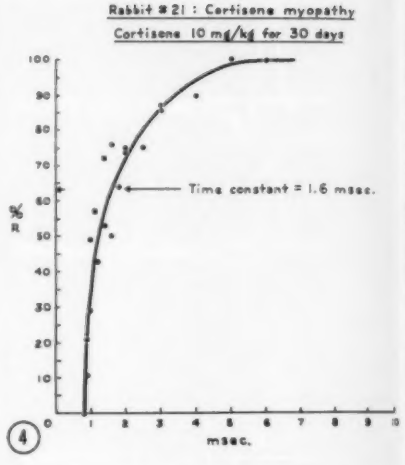


FIG. 3. Recovery curve of excitability in paravertebral muscle of rabbit following quinidine administration.
FIG. 4. Recovery curve of excitability in paravertebral muscle of rabbit with cortisone-induced myopathy.

solution administered intrathoracically produced a significant change. This is shown in the response curve of figure 3, which has a time constant of 2.9 msec. In the series of ten experiments with quinidine, it was found that the mean time constant was increased to 2.8 ± 0.3 msec., which is significantly different from the normal control value at a p level of less than 0.01.

A myopathy secondary to hypercortisonism was induced in 14 rabbits. Cortisone acetate was administered intramuscularly at a dosage of 10 mg. per kg. for periods of time varying from four to 40 days. The clinical features consisted of gradual appearance of extensive weakness, flaccidity, and atrophy of axial and appendicular somatic muscles, especially paravertebral, abdominal, and proximal limb girdle groups.

In these animals, time constant of recovery curve, determined from all experiments to be 1.6 ± 0.08, did not appear to vary significantly from normal, nor did the apparent absolute refractory period. A typical response curve is shown in figure 4. The measurements also did not show any changes relating to duration of cortisone administration.

Following the measurements each animal was sacrificed and specimens were taken for pathologic examination. Histologic study showed varying amounts of degeneration and regeneration of muscle fibers (figure 5), resembling in all details the alterations described recently by Ellis.[8] Necrosis usually was segmental within a muscle fiber, and the number of altered fibers varied from muscle to muscle within the same animal.

COMMENT

A summary of refractory period time constant measurements is presented in table 1. The increased refractory period induced by quinidine is a known effect and a basis for the pharmacologic utilization of this drug in depressing myocardial excitability.[4] The related drug, quinine, also produces the same effect[5] and is used in treatment of myotonic states. Since the quinidine effect was measurable by this method, the technic is sensitive enough to pick up changes of the order of magnitude of at least 1 msec.

Even though the severe muscle degeneration produced by hypercortisonism was confirmed histologically, the unchanged electrical excitability suggests preservation of enough normally responsive fibers or perhaps even normal segments of fibers. Actually, this is apparent histologically, also. It may be mentioned here that normal refractory period measurements have been obtained with this

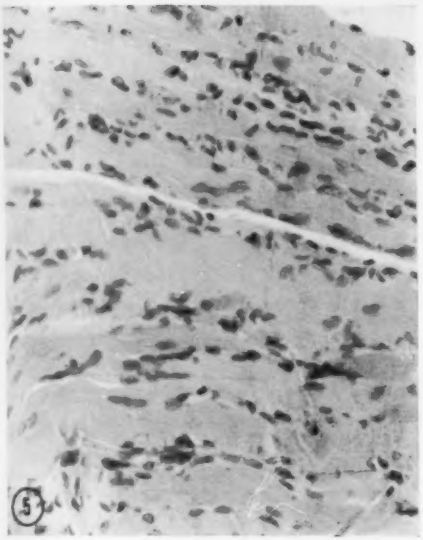


FIG. 5. Paravertebral muscle of rabbit administered cortisone acetate (10 mg. per day) for 30 days, demonstrating swelling and necrosis of muscle fibers and infiltration by histiocytes. The degeneration is spotty and segmental. Hematoxylin and eosin stain. x440.

method in human subjects with progressive muscular dystrophy and in mice with hereditary primary myopathy.[6] Again, the muscular degeneration is apt to be spotty and segmental in these conditions, and as long as some structurally normal fibers are present, it might be these fibers which are responsive, show normal excitability, and are consequently measured by the refractory period method. However, under other circumstances a spotty or segmental pathologic process might produce changes in excitability over the entire muscle fiber to which the above method would be quite sensitive. Evidence in favor of this possibility will be presented in another paper dealing with changes in refractory period in an experimental myopathy induced by potassium deficiency.[7]

In cortisone myopathy there is both massive necrosis and degeneration of fibers, as well as regeneration, going on at the same time. The cortisone-induced myopathy apparently is similar histologically to so-called Zenker's degeneration and also to that observed in vitamin E deficiency states, Coxsackie virus infections, and other conditions,[3,8] including potassium deficiency. It does not appear that the histologic status in these myopathies has any correlation with muscular excitability as measured by refractory period.

The mechanism of production of the cortisone-induced lesion is as yet unknown. It cannot be prevented by administration of potassium or vitamin E and does not appear to be related to secondary deficiencies of these substances, nor is it due to activation of a virus such as the Coxsackie.[3] The necrotic muscles secondary to hypercortisonism develop nonspecific chemical abnormalities similar in most respects to those described in many varied experimentally induced muscular lesions, especially those with wasting. Significantly, the muscles grossly lose potassium and gain in sodium.[3] However, it is of interest that, even with this apparent loss of muscle potassium, measurable changes in excitability do not occur in cortisone myopathy, even though such a change did occur in our animals given a diet deficient in potassium.[7] This may mean another mechanism is involved concerned with the availability of potassium for muscular excitability, and that this mechanism does not directly relate to histologic changes. Certain other related effects of cortisone on neuromuscular function[9] still remain unexplained: the worsening of myasthenia gravis during cortisone administration and improvement following withdrawal, the occasional relief of myotonia, and the occasional reduction of intensity of spasticity and fasciculations.

SUMMARY

A method of studying muscle excitability in terms of refractory period was developed, and measurements were made in normal rabbits

TABLE 1
REFRACTORY PERIOD TIME CONSTANT IN EXPERIMENTAL MYOPATHY

Experiment	*Time Constant (in msec.)*
Normal controls (12)	1.6 ± 0.1
Quinidine (10)	2.8 ± 0.3*
Cortisone myopathy (14)	1.6 ± 0.08

*Different from normal controls at p 0.01 level of significance.

during the effect of quinidine and in an experimental myopathy induced by hypercortisonism. Needle electrodes in paravertebral muscles were used for stimulation and recording. The action potentials evoked were studied oscillographically, and recovery of excitability was plotted in terms of relative responsiveness to a second stimulus. Control observations showed a time constant of refractory period of 1.6 msec., including an absolute refractory period of about 0.8 msec. Quinidine prolonged the time constant significantly and demonstrated the sensitivity of the method. Animals with metabolic myopathy following cortisone administration showed mainly severe muscle degeneration grossly and histologically and some evidence of regeneration. No changes in refractory period were found. The significance of these observations is discussed.

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■ If, as suggested, both sides of the brain are educated in expression, although the left is the leading side, I would still advocate the view I brought forward in the *Lancet*, with the important qualification that the right side may be the leading side for perception-educated sensations. So, then, we should have "crossed action" betwixt the two brains, and thus we might suppose a more perfect mental co-ordination. With regard to this, and to co-ordination in general, Hilton's law on the distribution of nerves from nerve trunks to joint, skin and muscle, and Brown-Sequard's researches on the relation of the motor and sensory nerves in the two sides of the cord, occur to us.

J. Hughlings Jackson in *Notes on the Physiology and Pathology of the Nervous System*, published in 1868.

Observations on hemiplegia with middle cerebral artery trunk occlusions and with "normal" carotid angiograms

J. E. Webster, M.D. and E. S. Gurdjian, M.D.

In a study of 200 hemiplegic or hemiparetic patients, there were 16 examples (8 per cent) of occlusion of the middle cerebral artery and 33 patients (16 per cent) having "normal" angiograms. This paper is an analysis of these two groups of patients in conjunction with neurologic and electroencephalographic studies, together with observations upon responses to compression of the carotid artery in the neck.[1–7]

MATERIAL

1. *Hemiplegic Patients with Main Trunk Middle Cerebral Artery Occlusion*

Occlusion of the middle cerebral artery trunk was usually found to be associated with profound hemiplegia, with or without aphasia.[8,9] The degree of paralysis was uniform and striking. Among 16 cases (table 1) there were two exceptions. These two patients, although having a complete occlusion of the trunk of the middle cerebral artery, had short lasting weakness of the opposite half of the body, from which each completely recovered. One was 30 years of age, with a trunk occlusion produced by clipping the middle cerebral artery in the removal of an aneurysm.

The electroencephalographic patterns commonly showed a delta activity, which also has been noted by Feiring and Sussman.[9] The blood pressure of these patients was often near normal. Such occlusions were due mainly to atherosclerosis rather than arteriolar sclerosis, which may be a more significant factor in the patients of group 2.

Carotid compression tests in these patients usually failed to induce syncope, whereas with occlusion of the anterior cerebral artery (or the carotid), syncope occurs in about 66 per cent upon compression of the contralateral carotid artery. In patients with occlusions of the middle cerebral trunk, this incidence is only 15 per cent (table 1). Such a difference in response must relate to the variations in the anatomic patterns of blood flow.

2. *Hemiplegic Patients with "Normal" Carotid Angiograms*

A far larger group than those with middle cerebral artery trunk occlusion were hemiplegic patients who presented "normal" carotid angiograms. Among 200 patients, 33 cases belonged in this category. As in group 1, contralateral carotid compression in the neck usually did not induce a syncopal response.

It is difficult to determine exactly the etiology of the hemiplegic state among patients with normal carotid angiographic patterns. The hemiplegic state with the grossly "normal" angiographic pattern may be due to an involvement of the smaller arterial branches supplying the internal capsule or a more widespread involvement of the smaller branches of the middle cerebral artery supplying the cortex and subcortex. Careful study of the angiographic pattern may show a complete filling of major vessels in such cases, but upon detailed inspection there may be multiple areas of atherosclerosis in primary and secondary branches. Among this latter group, there occasionally may occur a retrograde thrombosis involving the middle cerebral trunk and later the internal carotid artery in the neck, shown subsequently in repeated angiograms.

Other instances of "normal" carotid angiograms in the presence of a well-defined hemiplegia may be related to single or multiple at-

TABLE 1

MIDDLE CEREBRAL TRUNK OCCLUSION

Case	*Age*	*Sex*	*Neurostatus*	*EEG*	*Compression*	*Angiogram*
1	60	M	Rt. hemiplegia, severe, aphasia total. BP 115/90	Delta 2 lt. T-F, Dys. 2 lt. T-F	Rt.—0 Lt.—0	Lt. middle cerebral occlusion
2	56	M	Rt. hemiplegia, severe, aphasia total. BP 140/80	Delta 2 lt. T-F Dys. 2 lt. F-T-P	Rt.—syncope, Lt.—0 (Syncope due to sensitive carotid sinus reflex abolished by atropine gr. 1/100th)	Rt. middle cerebral occlusion
3	47	M	Rt. hemiparesis, mild aphasia. BP 150/100	Dys. 2 bioccip. max. lt.	Rt.—dizzy Lt.—0	Angiogram normal, 1 mo. later lt. middle cerebral occlusion (1 yr. car. thromb. lt.)
4	63	M	Rt. hemiplegia, severe, aphasia total. BP 115/90	Delt 2 lt T-F-P, Dys. 2 biF-T max. lt.	Rt.—0 Lt.—0	Lt. middle cerebral occlusion, lt. car. thrombosis
NOTE: Patient has occlusion of middle cerebral artery, with excellent cross-filling of anterior cerebrals and right middle cerebral but not left middle. Had chronic left carotid occlusion at bulb, as demonstrated by exploration of carotid.						
5	48	M	Rt. hemiparesis greater in arm, aphasia. BP 160/90	Delta 1 lt. T, Dys. 1 lt. T	Lt.—0 Rt.—syncope with conv. movements	Lt. middle cerebral artery occlusion
NOTE: Exception to general response.						
6	76	M	Lt. hemiplegia severe. BP 140/70	Dys. 1 gen'l.	Rt.—0 Lt.—0	Rt. middle cerebral occlusion. Partial carotid occlusion
NOTE: Massive shift of anterior cerebral artery with cerebral edema. Infarcted brain tissue removed. (Patient lived). Had syncope postoperatively on one occasion upon left carotid compression.						
7	62	M	Rt. hemiparesis, mild aphasia. BP 200/90 to 160/80	—	Rt.—0 Lt.—0	Lt. middle cerebral artery occlusion
8	56	F	Rt. hemiplegia, severe, aphasia, total. BP 150/60	—	Rt.—0 Lt.—0	Lt. middle cerebral artery occlusion
9	50	F	Lt. hemiplegia, severe. (Ruptured aneurysm, syphilis). BP 190/100	Delta 2 rt. T-F Dys. 2 biT-F, max. rt.	Rt.—0 Lt.—0	Lt. middle cerebral artery occlusion. Aneurysm rt. internal carotid
10	47	F	Lt. hemiplegia death. BP 140/80	Delta 2 rt. T, Dys. 2 gen'l. max. rt. T	Rt.—0 Lt.—0	Rt. middle cerebral occlusion. A single atheromatous plaque
11	30	M	Rt. hemiparesis, removal aneurysm. BP 120/70 to 130/80	Dys. 1 lt. T-F	Rt.—0 Lt.—0	Lt. middle cerebral artery occlusion (aneurysm)
12	64	F	Rt. hemiparesis, BP 155/95	Delt 1 lt. T	Rt.—0 Lt.—0	Lt. middle cerebral artery occlusion
13	62	F	Lt. facial weakness. BP 240/120	Delta 3 gen'l. Dys. 2 gen'l.	—	Rt. middle cerebral trunk occlusion
14	34	M	Lt. hemiparesis, BP 150/100	Normal	Lt.—0 Rt.—0	Rt. middle cerebral artery occlusion
15	65	F	Rt. hemiparesis, BP 150/90	Dys. 2 lt. hemi. Delta 2 lt. ant. and mid. T	Rt.—0 Lt.—syncope with heart block	Lt. middle cerebral occ. and rt. ant. cer.
16	41	M	Lt. hemiplegia, BP 108/72	—	Rt.—0 Lt.—0	Rt. middle cerebral artery occlusion

tacks of cerebrovascular insufficiency with a final irreversible cerebral ischemia, causes of which are not easily determined. Among patients with vertebral-basilar artery occlusive disease, there may early be a hemiplegic or hemiparetic state, without ophthalmologic findings. A carotid angiogram will thus appear "normal." Among this group, there is an eventual spreading of the paralysis to the opposite side of the body, the clinical state then becoming more typical of basilar artery occlusion. With the spread of the paralysis, carotid

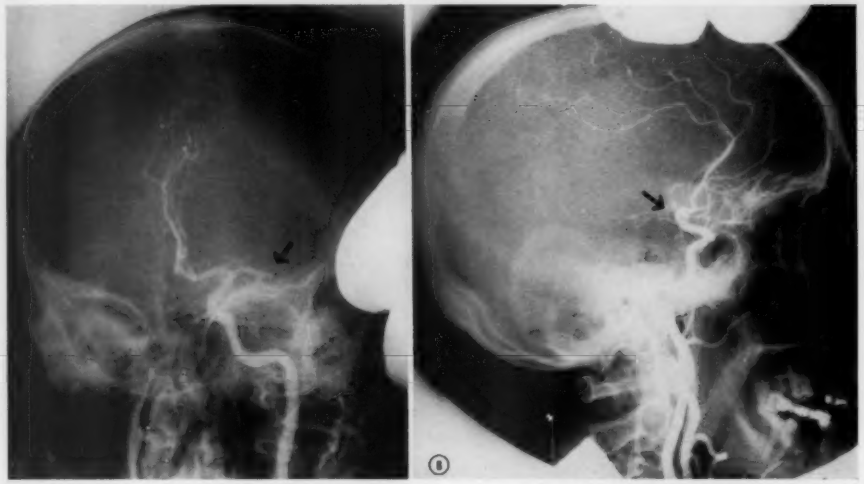

FIG. 1. Typical angiographic pattern of group 1 patients with occlusion of the middle cerebral artery trunk.

compression tests usually become positive. Patients with the paralytic residual from an embolus or emboli also may present "normal" angiographic patterns. Generally, group 2 consists of patients of more advanced age, often with associated chronic hypertension, renal, and myocardial disease. Electroencephalographic disturbances in this group usually are of a bilateral dysrhythmic pattern.

The carotid compression test among 33 cases resulted in syncope in five. Three of the five were found to have a carotid sinus reflex responsible for the syncope, prevented by the use of atropine. The incidence of syncope in this group, therefore, was about 15 per cent.

DISCUSSION

In an earlier paper, the responses to digital carotid artery compression in 100 hemiplegic or hemiparetic patients were analyzed.[6] In the preparation of this present paper, we have utilized the results of an additional 100 patients and find that the percentages in the 200 are essentially the same as in the first 100 cases analyzed. We find that digital carotid compression tests at the bifurcation give some clue

TABLE 2

SELECTED INSTANCES OF HEMIPLEGIC PATIENTS WITH "NORMAL" ANGIOGRAMS

Case	*Age*	*Sex*	*Neurostatus*	*EEG*	*Compression*	*Angiogram*
1	60	M	Rt. hemiplegia and aphasia. BP 240/140	Delta 2 lt. T-P, Delta 1 rt. occip., Dys. 2 gen'l.	Rt.—0 Lt.—0	"Normal" carotid angiogram. Small artery occlusion.
2	68	F	Rt. hemiplegia, no eye signs. BP 260/130	Dys. 1 biT, max. lt.	Rt.—0 (syncope later) Lt.—0 (syncope later)	"Normal" carotid angiogram. Ultimately developed basilar artery occlusion.
3	71	F	Spastic lt. hemiplegia. BP 130/100	Dys. 1 biT, max. lt.	Rt.—0 Lt.—0	"Normal" carotid angiogram. Atherosclerosis of secondary branches, both ant. & mid. cer. arteries.
4	47	M	Rt. hemiparesis, mild aphasia. BP 150/100	Dys. 2 bioccip., max. lt.	Rt.—0, dizzy Lt.—0	"Normal" carotid angiogram. Ultimately developed mid. cer. trunk occlusion, then carotid occlusion.
5	39	M	Mild lt. hemiparesis. BP 160/80	Dys. 1 biT-F	Rt.—0 Lt.—0	"Normal" carotid angiogram. Embolism with complete recovery.

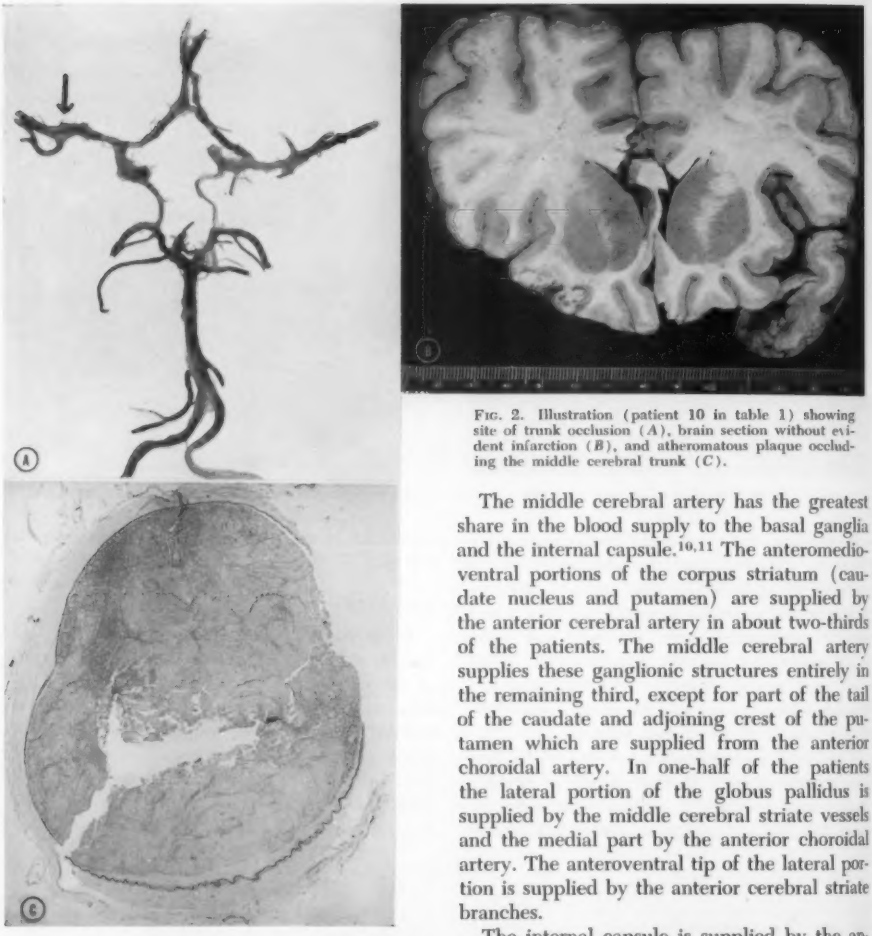

FIG. 2. Illustration (patient 10 in table 1) showing site of trunk occlusion (*A*), brain section without evident infarction (*B*), and atheromatous plaque occluding the middle cerebral trunk (*C*).

toward understanding the neurophysiologic basis for the neurologic state resulting from occlusion of the middle cerebral trunk or their terminal vessels (normal angiogram). When a well-defined hemiplegia is not associated with a syncopal effect on carotid bifurcation compression on the same side as the hemiplegia, a diagnosis of middle cerebral artery trunk occlusion or occlusion of the terminal vessels in the distribution of the middle cerebral (normal carotid angiogram) should be considered. The explanation for this may be found in the anatomic pattern of the cerebral circulation.

The middle cerebral artery has the greatest share in the blood supply to the basal ganglia and the internal capsule.[10,11] The anteromedioventral portions of the corpus striatum (caudate nucleus and putamen) are supplied by the anterior cerebral artery in about two-thirds of the patients. The middle cerebral artery supplies these ganglionic structures entirely in the remaining third, except for part of the tail of the caudate and adjoining crest of the putamen which are supplied from the anterior choroidal artery. In one-half of the patients the lateral portion of the globus pallidus is supplied by the middle cerebral striate vessels and the medial part by the anterior choroidal artery. The anteroventral tip of the lateral portion is supplied by the anterior cerebral striate branches.

The internal capsule is supplied by the anterior cerebral artery in the ventromedial portion of the anterior limb. The dorsolateral part of the anterior limb, the dorsolateral portion of the knee, and the dorsal part of the posterior limb are all supplied by the middle cerebral striate branches. The knee receives direct branches, usually two in number, from the internal carotid artery, and the ventral part of the posterior limb and the retrolenticular portions are supplied by the anterior choroidal artery. It has been shown that section of the anterior choroidal artery does not result in a paralysis.[12] Particularly among hemiplegics

FIG. 3. Angiographic studies illustrating a group 2 patient having "normal" angiograms with hemiplegia.

with normal angiograms, involvement of the capsular branches of the middle cerebral artery is likely. The blood supply to the hypothalamus from the middle cerebral artery is limited. The brainstem and the hypothalamus are supplied mainly by the basilar-posterior cerebral complex and the ganglionic branches of the anterior cerebral artery.

The observation that syncope does not usually occur in patients with a middle cerebral artery trunk occlusion, or among those with hemiplegia but with a "normal" carotid angiogram, suggests that the ganglionic branches of the middle cerebral artery do not subserve the conscious centers, which the anterior cerebral artery and the basilar-posterior cerebral complex fulfill.[13]

SUMMARY

1. Patients with hemiplegia or hemiparesis may frequently be found to have either an occlusion of the trunk of the middle cerebral artery or "normal" carotid angiograms.

2. When the middle cerebral artery distribution is involved in causing the hemiplegia, carotid compression tests are usually negative (compression of the carotid bifurcation on the side of the hemiplegia does not result in syncope).

3. This response is contrary to the syncopal state which usually occurs (80 per cent) upon contralateral carotid compression with occlusions involving the carotid, anterior cerebral, and basilar-vertebral vessels.

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CASE REPORT

Hemangioma of the skull associated with intracranial angioma

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THE ASSOCIATION of hemangiomas of the skull with similar lesions of the liver, kidney, spleen, brain, eye, adrenals, and other bones is an occasional postmortem finding.[1–8] The present paper is a report of a case of hemangioma of the skull which was associated with an angioma of the brain.

CASE REPORT

A 42 year old white housewife was admitted to the Bronx Municipal Hospital Center on July 6, 1957 because of dizziness, vomiting, and lethargy. For many years the patient had experienced recurrent occipital headaches of several hours' duration occurring one to four times a month. One month prior to admission the headaches began to increase in frequency. On the day of her admission she awakened asymptomatic, but several hours after breakfast she complained of dizziness accompanied by vomiting. Thereafter she suffered severe occipital headaches and became lethargic, whereupon she was brought to the hospital.

The personal and family histories were noncontributory. The patient never had seizures, motor or sensory disturbances, visual complaints, or mental changes.

Physical examination revealed a patient in acute distress, holding her head in pain and unable to cooperate fully. The temperature was 99° F., pulse 84 per minute, respirations 22 per minute, and blood pressure 124/84. There was moderate nuchal rigidity. A bruit synchronous with the pulse was heard by auscultation over the left eyeball. The bruit was eliminated by compression of the left common carotid artery. It was not heard by the patient. There were no palpable masses in the scalp. The right pupil measured 4 mm., the left 2 mm.; both reacted to light and accommodation. The ocular excursions were normal. Bilateral retinal, peripapillary, circular hemorrhages were seen. The optic disks were not elevated. Visual fields by gross confrontation suggested a right homonymous hemianopia. The remainder of the general physical and neurologic examination was normal.

Laboratory data. Blood examination revealed a white blood cell count of 15,950 per cu. mm., with a differential of 89 per cent polymorphonuclears, 9 per cent lymphocytes, and 2 per cent monocytes. The hemoglobin was 13.6 gm. per cent and the hematocrit was 40 per cent. Blood urea nitrogen was 15 mg. per cent and fasting blood sugar was 88 mg. per cent. Urinalysis was normal. Lumbar puncture on admission revealed an initial pressure of 250 mm. water. The cerebrospinal fluid was uniformly blood-tinged in six tubes, and the closing pressure was less than 30 mm. water. There were 13,500 red blood cells per cu. mm. and 60 white blood cells per cu. mm. The supernatant cerebrospinal fluid was clear. The cerebrospinal fluid protein was 43 mg. per cent and the cerebrospinal fluid sugar was 78 mg. per cent.

There was a mildly diffuse abnormal electroencephalogram, with no focal or paroxysmal signs.

Roentgenographic examination of the skull showed an oval, radiolucent area in the mid-upper occipital bone, measuring about 2.5 cm. in its greatest diameter. Fine stippling and honeycombing were present within the translucent area. There was no reactive sclerosis about the lesion (figures 1 and 2). Lateral stereoscopic and lateral laminographic films of the skull demonstrated no evidence of destruction or bulging of either table of the skull. The pineal gland was not calcified. Cranial vascularity was normal. There was no abnormal intracranial calcification.

Hospital course. On July 8, 1957 a carotid angiogram was performed by the injection of 35 per cent Hypaque into the left common carotid artery. In the lateral and anteroposterior films (figures 3, 4, 5, and 6) a large intracranial angioma of the left parietal region was seen, supplied by several large tortuous vessels arising from the left middle cerebral group. There was no filling of the anterior cerebral vessels. A connection between the angioma and the hemangioma of the skull could not be demonstrated.

The following day a right carotid angiogram was performed. The right anterior cerebral artery and right middle cerebral artery filled normally. There was no anastomosis between these vessels and the left parietal angioma. At this time the left carotid artery was compressed and there was also filling of the left anterior cerebral artery; the left middle cerebral vessels filled with radiopaque

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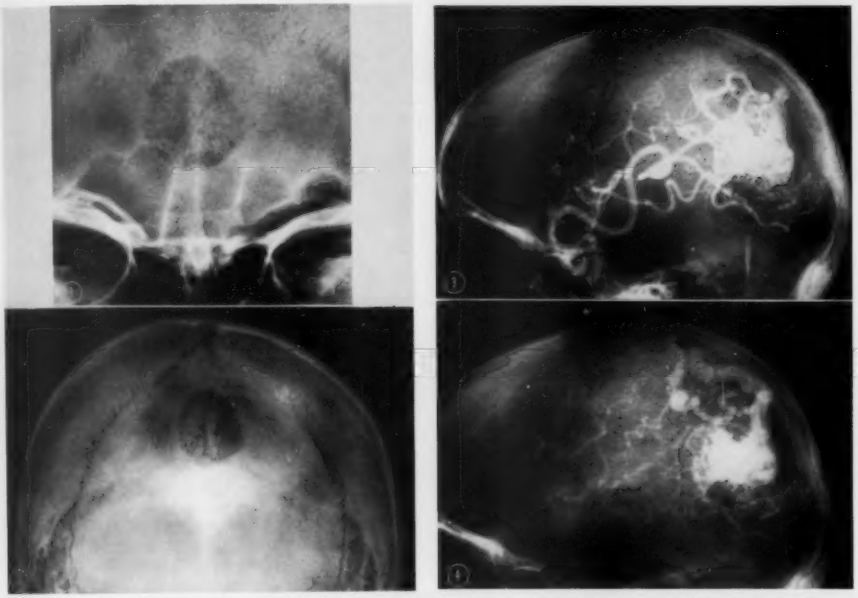

FIG. 1. Anteroposterior film of the skull shows the hemangioma in the mid-upper occipital bone, measuring about 2.5 cm. in greatest diameter. It has a typical x-ray appearance: radiolucent area, finely stippled, with no reactive sclerosis about it.

FIG. 2. Towne view of the skull shows the detail of the lesion better. The slightly irregular, "honeycomb" rim is most likely due to invasion of the normal bone by the cavernous hemangioma. The vertical streak of radiolucency represents a portion of the sagittal suture projected onto the hemangioma in this view.

FIG. 3. Lateral cerebral angiogram, after injection of Hypaque into the left common carotid artery, shows the large arteriovenous anomaly in the left parietal region. The lesion is fed by several large, tortuous vessels of the middle cerebral group. The cerebral angioma has no demonstrable connection with the skull hemangioma.

FIG. 4. Lateral cerebral angiogram, a second later than that of figure 3, shows drainage into several large veins with no evidence of opaque medium in the region of the skull hemangioma.

material to a lesser extent. There appeared to be a faint opacification of the angioma.

Following cerebral angiography the patient continued to improve. The right homonymous hemianopia with macular sparing was confirmed by perimetry on July 19, 1957. This was the only deficit noted when she was discharged August 2, 1957. She was functioning normally when last seen August 29, 1957.

DISCUSSION

A syndrome consisting of chronic periodic headaches, intracranial bruit, and subarachnoid hemorrhage, with preservation of ocular and trigeminal function, may often be observed in cases of intracranial angioma.[9,10] In this instance, angiography demonstrated such a lesion in the left parietal region.

The finding of a radiolucent area in the mid-occipital bone consistent in appearance with a hemangioma of the skull was the striking and unusual feature in this case. There was no apparent anatomic connection between this bone lesion and the cerebral angioma.

The differential diagnosis of the occipital lesion included epidermoid tumor, a leptomeningeal cyst, a meningioma, and an eosinophilic granuloma, all of which usually have features not seen in the skull films of this case.

Hemangiomata of the skull are rare tumors, comprising 0.7 per cent of all osseous neoplasms. Wyke[11] found the primary hemangiomas made up only 0.2 per cent of osseous neoplasms and 10 per cent of primary benign neoplasms of the skull. They may be found in any bone of the skull, and are usually cavernous, almost always benign, and most commonly present in middle-aged females.[11–15]

Of the 61 cases of hemangiomas arising in the skull, Wyke[11] found ten cases in which

FIG. 5. Anteroposterior left cerebral angiogram again shows filling of the parietal vascular anomaly by way of large abnormal vessels of the middle cerebral group with large draining veins.

FIG. 6. Anteroposterior right cerebral angiogram, with compression of the left carotid artery, shows filling of the right anterior and middle cerebral groups, normal in appearance. There is filling of the left anterior cerebral group and even some filling of the left middle cerebral vessels with faint opacification of the left parietal vascular anomaly.

hemangiomas were existent in other parts of the body. The liver seems to be a favored site, with the spleen, kidney, and adrenals also being involved. Some of the cases reported by other authors appear to be examples of Lindau's disease[4] or variants of Sturge-Weber's syndrome.[2,16,17] In one case,[3] there was pathologic verification of involvement of the brain, while in two others[8,15] there was solely clinical evidence of brain involvement by angiomas.

There are numerous extensive studies of intracranial angiomas in the literature[9,10,18–20] without plain skull roentgenographic changes suggestive of hemangiomas of the bone.

SUMMARY AND CONCLUSION

A presumptive case of hemangioma of the occipital bone associated with intracranial angioma documented by angiography is reported. There was no apparent anatomic connection between the lesions. However, it is believed that intracranial angiomas, as well as angiomas in other organs, may occur in association with hemangiomas of the skull in rare instances.

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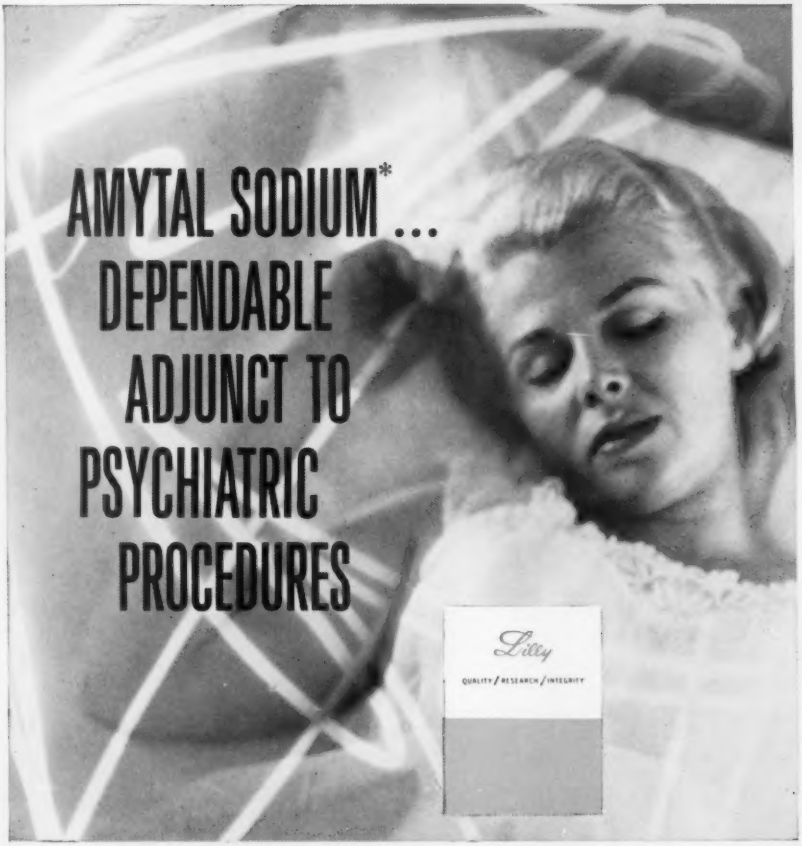

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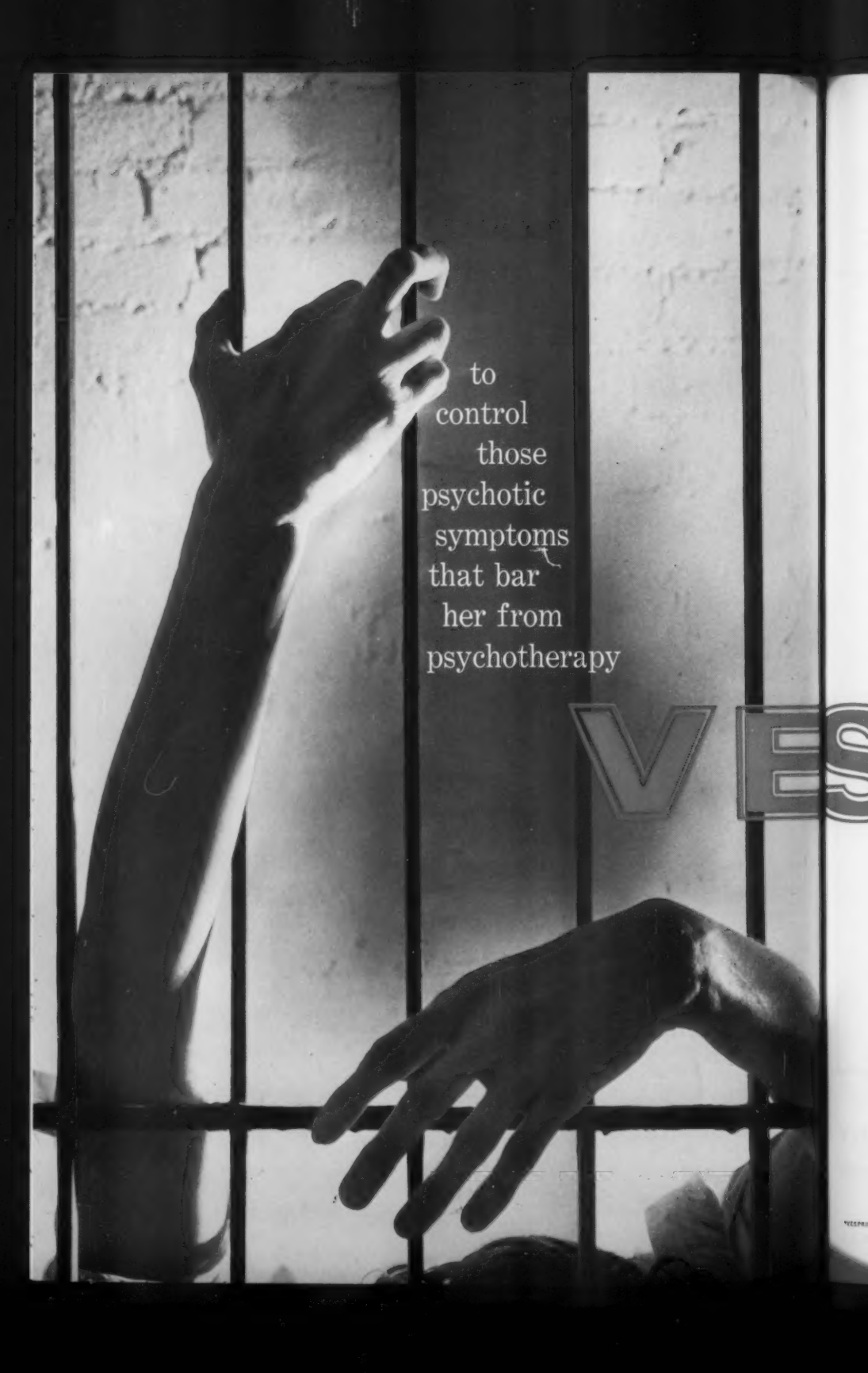
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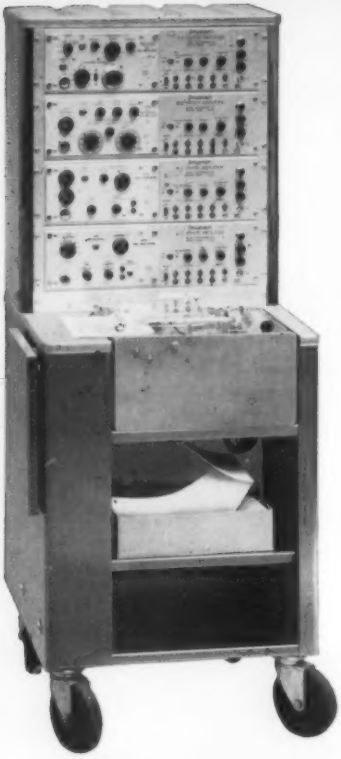

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AUGUST 1958

ANA Holds Its Eighty-Third Five hundred and seven neurologists and scientists attended the eighty-third annual meeting of the American Neurological Association in the Claridge Hotel, Atlantic City (June 16-18). Forty-two scientific papers and five demonstrations were presented. Included in the compact program were I. S. Wechsler's presidential address, "Critical Consideration of the Status of Neurology," and dissertations on "kuru" disease, a new neurologic disorder found among a tribe of natives in New Guinea, reminiscent pathologically of Jacob Creutzfelt's disease; clinical evidence of baroceptors in the human dura (Pollock and Kessert); the laminar destruction by high energy deuterons within different layers of the cerebral cortex (Malis, Kruger, and Rose); visualization of the vascular system of the spinal cord by means of maceration of specimens injected with vinyl (Gillilan); cerebellar atrophy in patients suffering from chronic alcoholism (Victor, Adams, and Mancall); the reduction in brain volume after use of urea (Javid); hemorrhagic encephalopathy in experimental hypernatremic conditions (Luttrell and Finberg); and an extensive analysis of lipids in the human cerebrospinal fluid (Tourtellotte, Parker, Skrentny, and DeJong).... The scientific demonstrations included the use of focused ultra sound in neurologic research (Ballantine and Bell); the technic of transillumination for the demonstration of cerebral defects (Dodge, Porter, and Luessenhop); thalamus, cortex, and visceral brain in cerebral disorders (Papez); early treatment of ruptured intracranial aneurysms (Pool); and the formation of myelin forms in brain tissue-effect of surface-active substances (Ayres).... The annual ANA dinner was held Tuesday night, June 17.... The eighty-fourth annual meeting of the American Neurological Association will be held at the Claridge Hotel, Atlantic City, June 15-17, 1959.

New ANA Officers and Members Bernard J. Alpers became the new president of the American Neurological Association at the eighty-third annual meeting; Derek Denny-Brown was named president-elect; Paul I. Yakovlev, first vice-president; and Margaret A. Kennard, second vice-president; Charles Rupp continues as secretary-treasurer and editor of Transactions, and William F. Caveness as assistant secretary. Elected to active memberhip were Edward C. Clark and C. Wesley Watson; to associate membership, Jordi Folch-Pi, Lois A. Gillilan, Tryphena Humphrey, Alfred Pope, Karl Pribram, and Heinrich B. Waelsch; and to corresponding membership, Victor Soriano.

Neuropathologists and MS Group Meet Preceding ANA

The American Association of Neuropathologists and the Medical Advisory Board of the National Multiple Sclerosis Society held their annual meetings on the day preceding the ANA meeting (June 15). The former featured a symposium on the encephalomyelopathies in infancy and childhood, which was directed by K. L. Scharenberg, and included a review on perinatal infectious diseases (Wolf and Cowen), a study of kernicterus in the rat (Blanc), and the effects of asphyxia on the brain and spinal cord of newborn monkeys (Windle). The sessions of the MS Medical Advisory Board highlighted a presentation by Albert B. Sabin on the status of the alleged virus of multiple sclerosis (Margolis and Shubladz), and the presentation of a new viral hypothesis for multiple sclerosis.

Nachmansohn Organizes Fellowship Program in Neurochemistry

Under the sponsorship of the National Institute of Neurological Diseases and Blindness, a postdoctoral training program in neurochemistry has been organized by David Nachmansohn of the departments of biochemistry and neurology, College of Physicians and Surgeons, Columbia University. The program provides for several fellowships of two to three years for those who wish to broaden their background in general biochemistry and become familiar with current problems in neurochemistry and neurochemical research. General training is offered through courses and seminars by outstanding investigators in advanced theories and methods of biochemistry and physical chemistry.... A doctor's degree in chemistry, biology, or medicine is required for enrollment. The amount of each fellowship stipend is geared to previous experience.... For information and application forms, communications should be sent to Dr. David Nachmansohn, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York 32.

Italian Neurologists To Meet in Messina

The thirteenth national congress of the Italian Society of Neurology and the annual meeting of the Italian Society of Electroencephalography will be held in Messina (May 7-10, 1959). The scientific sessions are divided into three symposia, to be followed by the proceedings of the annual meeting of the Italian Society of Electroencephalography. There will be a symposium on degenerative diseases of the central nervous system, chaired by Professor P. Ottonello, with R. Rossini, G. C. Cavalca, and E. Chiaramonti serving as relators; another symposium on dystrophies and protopathic muscular atrophies will be under the chairmanship of Professor G. Pintus, with G. A. Buscaino, P. Sarteschi, and V. Bergamini serving as relators. There also will be a neurosurgical symposium on pseudotumoral encephalopathies. The chairman of this symposium is Professor G. B. Belloni, and the relators are P. Grugoni and G. Campailla.... Applications for attendance at the neurologic society meeting, as well as titles of communications, should be sent to Professor D. Pisani, Chairman of the Organizing Committee, via Garibaldi, Palazzo I.N.A.I.L.

Messina, Italy. Tiles of communications to be submitted for the meeting of the EEG society should be forwarded to Professor Mario Gozzano, via Archimede 62 Rome, Italy. The deadline for the titles of communications with brief summaries and the texts of reports is January 31, 1959. The registration fees are 3,000 lira ($4.84) for the members of the Italian Society of Neurology, 5,000 lira ($8.06) for non-members, and 2,000 lira ($3.23) for guests.

Grashchenkov Visits The United States Academic Professor N. I. Grashchenkov, prominent Moscow neurologist, recently visited the USA as a delegate of WHO. Included in his itinerary was the University of Minnesota, the meeting of the American Neurological Association in Atlantic City (June 16-18, 1958), and the National Institute of Neurological Diseases and Blindness (June 23). Professor Grashchenkov is the author of Russia's Sixth Five-Year Plan for Neurology (see April 1958 Newsletter); during his visit to NINDB he expressed interest in greater international collaboration to solve some of the major current problems in neurology, such as cerebrovascular disease, infectious diseases of the nervous system, and geographic pathology.... Besides his high standing as a neurologist, Grashchenkov also ranks high in the medical hierarchy of the USSR. He is director of the Department of Biological Sciences of the Academy of Sciences USSR, director of the Division of Physiology and Pathology of the Sense Organs of the All-Union Institute of Experimental Medicine, and has the Chair of Nervous Diseases of the Central Institute for the Advanced Training of Physicians.... The leading institutes dealing with neurologic problems in the USSR are: Moscow: Institute of Neurology, Academy of Medicine Sciences USSR (Director, Prof. N. V. Konovalov); Institute of the Brain (Director, S. A. Sarkisov); Institute of Neurosurgery im. Burdenko (Director, B. Egorov); Department of Clinical Neurology of the First Moscow Medical Institute im. Sechenov (Director, I. N. Grashchenkov). Leningrad: Institute of Neurosurgery im. Polenov (Director, V. N. Shamov). Kiev, Ukr SSR: Institute of Neurology (Director, Dr. Arutyunov). Tbilisi, Georgian SSR: Institute of Experimental and Clinical Neurology (Director, P. M. Saradzhishvili).

Sechenov Can Now Be Read in English The upsurge of interest in Russian scientific accomplishments has called for a translation and re-publication of a number of Russian scientific journals. Among them is the Sechenov Physiological Journal of the USSR, the contents of which include much neurophysiology. The English language Sechenov is published by the Pergamon Institute, whose offices are: 122 East 55th Street. New York 22, and 4-5 Fitzroy Square, London W.I., England. Private subscription to the Sechenov is $45 a year.... The Sechenov is one of the eight translated journals published under contract with the National Institutes of Health, Public Health Service, and is being distributed without charge to the libraries of some 400 medical schools and research institutes throughout the United States. Its

translation and publication conform with the wish of the Senate Appropriations Committee "to promptly make available to American scientists the full findings of Russian scientists".... There has been considerable interest in the publication of an English translation of the Pavlov Journal of Higher Nervous Activity, and the National Institutes of Health plan to sponsor this during the coming year.

AAN and ANA Approve WFN Constitution and Officers In executive sessions at their annual meetings of 1958, the AAN (April 23-26) and the ANA (June 16-18) approved the provisional constitution and officers of the World Federation of Neurorolgy (See October 1957 Newsletter). So far, the following 20 countries have joined the WFN: Argentina, Belgium, Bulgaria, Cuba, Czechoslovakia, Denmark, France, Germany, Great Britain, Iran, Italy, Norway, Peru, Poland, Romania, Sweden, Switzerland, Turkey, United States, and Uruguay. The officers of the WFN are: president, Ludo van Bogaert (Belgium); vice-presidents, Auguste Tournay (France), and Macdonald Critchley (Great Britain); secretary-general, Pearce Bailey (U.S.A.); chairman of the committee on constitution and bylaws, Georges Schaltenbrand (Germany).

Sixty-one Added to AAN Membership Sixty-one physicians and scientists have been added to the membership roster of the AAN since May 1958. Included are four active, 33 associate, and 24 junior members. These are: Jay B. Angevine, Erna D. Ball, Andre Barbeau, Donald W. Baxter, Flora Herman Biele, Raymond N. Bieter, Richard I. Birchfield, Julio R. Borges, Joseph C. Borrus, Paul Bratty, S. R. Brownstein, Joel Brumlik, Caridad Cruz, A. J. de Lorenzo, Edmund deMaar, Edwardo Derobertis (Buenos Aires), Allan W. Downie, Leon Eisenberg, Raul Espinosa, William Feindel, J. Paul Fitzgibbon, Archibald Foley, John D. French, Ahmed Frugh, David Goldblatt, Juan Antonio Gomez, Michael P. Goodson, Frank Gorham, Soloman Hakim, Elizabeth C. Hartman, Arthur J. Heather, Alanson Hinman, William Ingram, Jr., Marion F. Jurko, David Kennedy, Marvin C. Korengold, Lucille Loeser, John C. Lychak, Marion C. McKee, Manuel Mier, Harilaos Mikropoulos, Yusuf Onel, Celestino A. Panero, Nicholas Papadopoulos, George W. Paulson, Virginia L. Payne, Reuben Rabinovitch, Renato Ricca, Ruth A. Rice, Ralph W. Richter, Richard Satran, Margaret R. Seiden, Henry K. Shoemaker, Joseph U. Toglia, Ann Marie Travis, Martin H. Triedman, David P. Tyler, Eduardo Vallejo, Hirsch Wachs, Stuart Weiss, and Irwin B. Wilson.... The total AAN membership is 1,890, of which nine are honorary, 52 honorary-corresponding, 769 fellows and actives, 727 associate, and 333 junior members.... Inquiries on AAN membership should be sent to Dr. Pearce Bailey, Chairman, AAN Membership Committee, National Institutes of Health, Bethesda 14, Maryland.

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Zier, A. and Doshay, L. J.: Procyclidine Hydrochloride (Kemadrin) Treatment of Parkinsonism in 108 Patients, Neurology (July) 1957.

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Lerner, P. F.: Kemadrin, a New Drug for Treatment of Parkinsonian Disease, J. Nerv. & Ment. Dis. 123:79 (Jan.) 1956.

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There are several fellowships available for periods of 2 to 3 years. This stipend is dependent on previous experience. A doctor's degree in chemistry, biology or medicine is prerequisite. For application or information write to:

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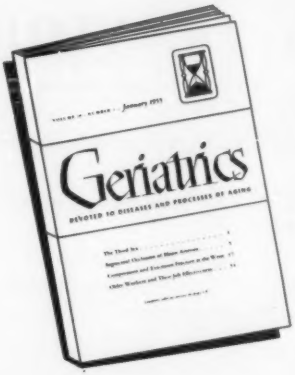

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1. Graffagnino, P. N., Friel, P. B. and Zeller, W. W.: Emotional disorders treated with meprobamate and promazine. Connecticut M. J. 21:1047, Dec. 1957.

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(hospitalized patients—all types)

by disease

DIAGNOSIS	NO. OF PATIENTS	NO. IMPROVED
SCHIZOPHRENIA		
PARANOID	7	2
NON-PARANOID	45	34
DEPRESSION		
PSYCHOTIC†	37	25
NEUROTIC	16	10
ANXIETY STATE	9	8
CHARACTER DISORDERS	15	13
OTHERS	16	13
TOTALS	145	105

by symptom

SYMPTOM	NO. IMPROVED
SLEEP DISTURBANCES	36
ANXIETY	30
TENSION	31
AGITATION	8
OTHERS	11
TOTAL	116

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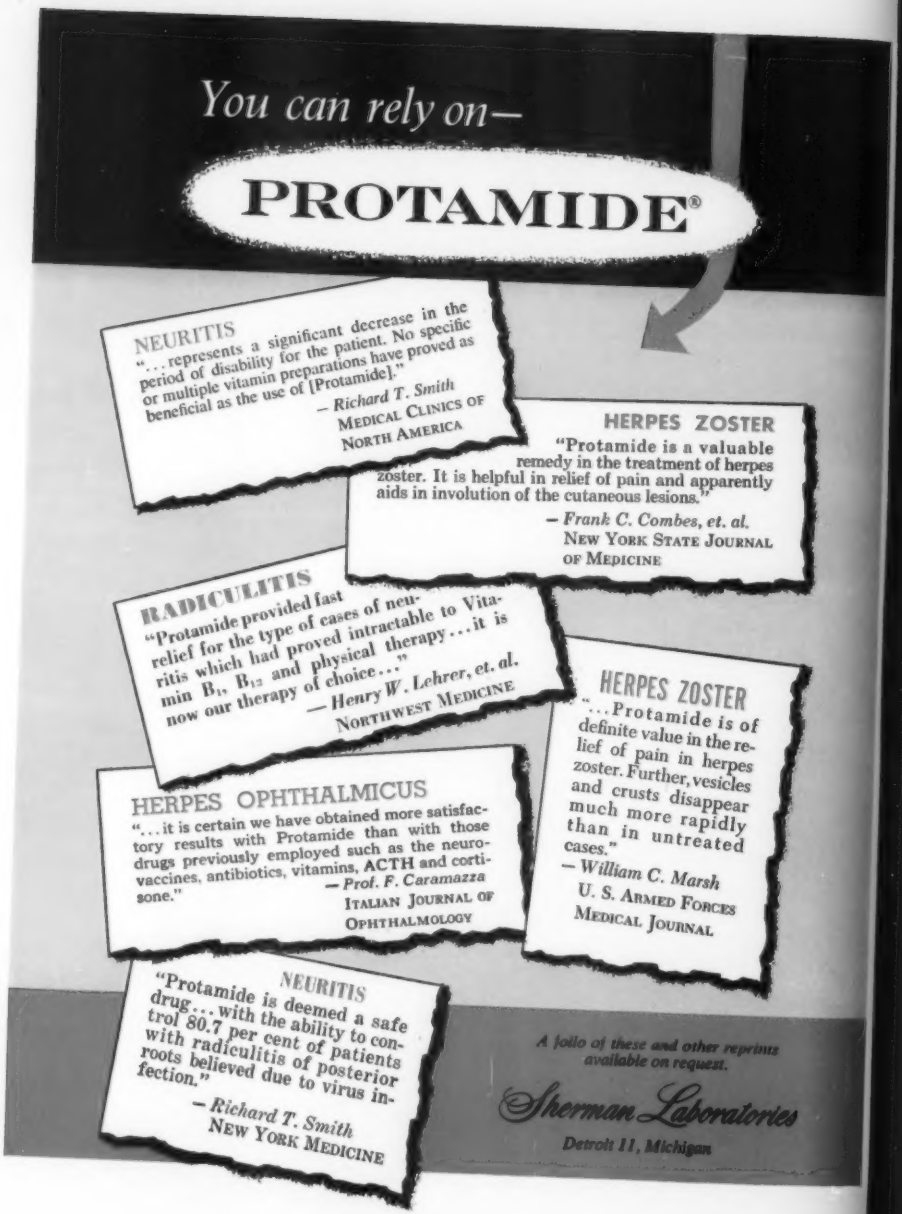
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